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CONTENTS

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SOCIAL FACTORS IN THE AETIOLOGY OF NEPHRITIS IN CHILDHOOD

BY

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(RECEIVED FOR PUBLICATION FEBRUARY 6, 1956)

In view of the fact that nephritis is so often preceded by infection, usually in the upper respiratory tract, it is to be expected that factors favouring the spread of respiratory infection will also raise the incidence of nephritis. A recent study of nephritis in childhood has produced evidence that the incidence rises quite steeply as we descend the social scale and suggests that overcrowding is the feature of poverty which is most likely to be significant. As little has been published on this aspect of the aetiology of nephritis the results of this study are presented here.

Case Material

The case material for this study, consisting of 265 consecutive cases of nephritis admitted to the Royal Aberdeen Hospital for Sick Children between April, 1934, and May, 1952, has been briefly described in a previous paper (Clark, 1956).

Incidence in Relation to Social Class

In 130 cases it is impossible from the information in the notes to assess the social status of the father with certainty. In a further 16 cases the child was maintained by the mother alone because of illegitimacy, or death or divorce of the father. Table 1 shows the distribution of the remaining 119 cases according to the social class of the father (General Register Office, 1951).

TABLE 1
INCIDENCE AND SOCIAL CLASS

Social Class	Number of Cases
I	0
II	12
III	28
IV	37
V	42
Total	119

Perusal of the addresses from which the remaining children were admitted suggests that the 119 cases are probably a fairly representative sample of the whole series in respect of social class.

According to the Annual Reports of the Registrar-General for Scotland (1946 to 1952—the only years for which the figures for total births are analysed according to social class), the ratio of births in the five social classes in Scotland is of the order of 3, 10, 53, 21, 12, and it is obvious, therefore, that an unduly high proportion of these cases of nephritis came from social classes IV and V. Where the home circumstances are poor, this will, of course, weigh heavily with the family doctor in his decision on whether the child should be admitted to hospital or not, and it is always difficult to assess to what extent this will bias the hospital figures in favour of cases from the lower social classes. The excess of cases in social classes IV and V shown in Table 1 is so great, however, that I find it difficult to believe that it does not, in part at least, represent a real increased incidence of nephritis in these social classes.

I have found no comparable series of cases of nephritis in which the incidence in relation to social class is discussed, but Hewitt and Stewart (1952) found a similar social gradient in the incidence of acute rheumatism in childhood, a finding of some interest in view of the relationship of both diseases to streptococcal infection. After careful study of the social factors involved in 793 Sheffield children suffering from a first attack of acute rheumatism they found no evidence that the disease was related to bad housing or poverty *per se* and concluded that the increased exposure to infection associated with large families and overcrowded homes might be responsible for the social gradient observed. This view and its applicability to nephritis will be further discussed in the next section.

Incidence in Town and Country

Of the 265 cases, 160 lived in the City of Aberdeen and 74 in the remainder of the County of Aberdeen.

Thirty-one came from outside Aberdeenshire. When these figures are related to the respective populations of the City and County of Aberdeen, a marked difference in incidence is seen.

A study of the Annual Reports of the Registrar-General for Scotland shows that throughout the period of the survey there has been a steady tendency for the population of the City to rise and for the population of the remainder of the County to fall. While there have been some fluctuations from time to time, it is probably sufficiently accurate for the present purpose to take as the population of each area the average of the figures for the first and the last years of the survey. Table 2 shows the population figures and the number of cases of nephritis over the whole period per 100,000 of the population.

TABLE 2
INCIDENCE IN CITY AND COUNTY OF ABERDEEN

	Population			Cases of Nephritis in Children	Cases per 100,000 Total Population
	1934	1952	Average for 1934 and 1952		
City of Aberdeen ..	171,918	183,626	177,772	160	90
Remainder of County of Aberdeen ..	148,210	143,056	145,633	74	51

While this table offers a useful means of comparison between the two areas it does not, of course, give any indication of the absolute frequency of nephritis in children in either town or county, for the cases of nephritis are drawn only from children under 12 years of age and not from the total population. Its validity as a means of comparison, therefore, depends on the assumption that the proportion of children in the two populations is approximately the same. Figures for the actual child population are readily available for two years only, 1948 (Craig and Burrell, 1950) and 1951 (General Registry Office, Edinburgh, 1953). These figures show that children under 12 years of age constituted 18·5% of the total population of the City in 1948 and 18·7% in 1951, while the corresponding figures for the remainder of the County were 21·3% and 21·7%. If this proportion of children in the two populations has remained constant throughout the period of this survey the true difference in incidence of nephritis between town and county children must be rather greater than the figures in Table 2 suggest.

It may be suggested that in the City there is a greater tendency to make use of the hospital services because of their proximity and that in consequence a higher proportion of the total cases are sent to hospital from the City than from the County. It is obvious that this does not explain the observed difference in incidence if we consider the number of cases admitted from Fraserburgh and Peterhead, the only towns in Aberdeenshire with populations of over 10,000, apart from the City of Aberdeen itself. The combined population of these two towns has remained virtually static during the period of the survey, the average for the years 1934 and 1952 being 23,125. From this population 21 children have been admitted with nephritis, an incidence of 91 per 100,000, practically the same as the figure for Aberdeen City.

If we now consider the figures for the County of Aberdeen after excluding the towns of Fraserburgh and Peterhead as well as the City of Aberdeen, we find that 53 children have been admitted with nephritis out of a total population of 122,508, an incidence of 43 per 100,000. It thus appears that, in this region, nephritis is at least twice as common in children living in a city or town as in children from rural surroundings.

I have found no previously reported series of cases of nephritis analysed according to place of residence, but Hewitt and Stewart (1952) have reported a similar high incidence of acute rheumatism in city children. In a study of the notification rates in certain regions of England where notification of acute rheumatism is compulsory, they found that the annual rate in Sheffield was between two and three times the rate in a rural area of Lincolnshire. As they point out, 'the variation exhibits the polarity usually found in infectious diseases, with the highest risk in the most densely populated area and the lowest risk in the most dispersed community'. Thus the present series of cases of acute nephritis and Hewitt and Stewart's cases of acute rheumatism bear a close resemblance to one another in respect both of incidence in relation to social class and of incidence in relation to urban versus rural domicile. As mentioned above they concluded that overcrowding with consequent increased exposure to infection was the most important factor in determining the distribution of their cases, and it is reasonable to suggest that the same factor is at work in the case of nephritis. Details of the home circumstances are unfortunately not available in the majority of my cases, but an interesting parallel emerges when we compare the relative incidence of nephritis as shown in Table 2 with the relative frequency of overcrowding in the areas concerned. Table 3 shows the figures for the incidence of nephritis in Aberdeen City, the remainder of Aberdeenshire and the towns of Fraserburgh and Peterhead compared with figures indicative of the

frequency of overcrowding derived from the 1951 census figures (General Registry Office, Edinburgh, 1953).

From this table it is clear that Fraserburgh and Peterhead resemble Aberdeen City not only in the incidence of nephritis but also in the incidence of overcrowding and that in both respects the rural areas present a very different picture.

TABLE 3

INCIDENCE OF NEPHRITIS IN RURAL AND URBAN AREAS OF ABERDEENSHIRE

	Cases of Childhood Nephritis per 100,000 Total Population	Percentage of Households Occupying		Percentage of Households containing More than 2 Persons per Room
		1 Room	2 Rooms	
Aberdeen City ..	90	9·9	28·2	8·1
Remainder of Aberdeen County	51	3·8	13·2	4·9
Fraserburgh }	91	13·1	26·1	12·9
Peterhead }		9·0	25·1	10·8

It is generally accepted that respiratory infection, and in particular streptococcal infection, is the precipitating cause of most cases of nephritis and it seems highly probable that intimate contact is the most important factor favouring the spread of such infections (Dingle, Rammelkamp and Wannamaker, 1953); it seems reasonable, therefore, to conclude that the higher incidence of nephritis found in the larger towns and in the lower social classes is related mainly, if not entirely, to the frequency of overcrowding.

Summary

It is shown that, of children admitted to hospital with nephritis in north-east Scotland, an unduly high proportion come from families belonging to social classes IV and V.

It is further shown that the incidence of nephritis among country-dwelling children is only half that in children living in the City of Aberdeen or in the only two towns in the region with populations of over 10,000. The incidence of nephritis is closely paralleled by the incidence of overcrowding in the respective areas, and it is suggested that overcrowding, with resulting increased opportunities for the spread of infection, is the aspect of poverty which is most likely to be responsible for the higher incidence of nephritis in children from poorer homes.

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THE PROGNOSIS OF NEPHRITIS IN CHILDHOOD

BY

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It has long been recognized that comparatively few cases of nephritis in childhood die in the early stages of the disease and it is widely believed that the great majority of cases recover completely. Hebert (1952) has summarized the results of many of the long-term studies of nephritis in childhood published in the British and American literature in the past 30 years. In the majority of these reports complete recovery was claimed in from 70% to 97% of the survivors from the acute illness. Only four of the reports quoted were published in this country and of these only one (Giles, 1947) has appeared in the last 20 years. I have found three additional papers on this subject in the British literature in that period (Cass, 1939; Tallerman and Burkinshaw, 1939; Payne and Illingworth, 1940). Tallerman and Burkinshaw (1939) and Giles (1947) support the majority view that over 70% of cases recover completely. Cass (1939) found 64% healed of 88 cases with an acute haemorrhagic onset. On the other hand, Payne and Illingworth (1940) found evidence of active or latent disease in 62 out of 89 cases seen from one to 12 years after the initial attack. Their findings support a minority view, strongly held in America, that the long-term prognosis in nephritis is much poorer than is popularly supposed, and with Snoke (1937) they maintain that a failure to recognize the latent stage has been responsible for undue optimism in many of the published reports claiming a high proportion of complete recoveries. Snoke, indeed, claimed that 'no patient who has had nephritis can be considered as healed until repeated quantitative studies of concentrated urine, i.e., Addis counts, have given the kidney a clean bill of health'. On this basis he considered that only 57 of 154 patients followed up had healed completely. Murphy and Rastetter (1938) found a very similar recovery rate in a study of 105 patients under 30 years of age. In a subsequent paper published from Rochester, however, Snoke (1939) reported a very different long-term prognosis; here, using the same standards of cure, he found a recovery rate of 72% in 106 patients as compared with 37% in his original series reported from Stanford University Medical School. He suggested that sampling and a geographical difference in the manifestations of nephritis might explain this discrepancy.

Because of these differences of opinion and in particular of the extremely poor prognosis suggested by Payne and Illingworth (a view which, so far as I know, has been subsequently contradicted in this country only by Giles (1947)), it appears worth while to present the results of a follow-up study of 265 consecutive cases of nephritis admitted to the Royal Aberdeen Hospital for Sick Children between 1934 and 1952.

Material

The case material for the present study has been briefly described in a previous paper (Clark, 1956) in which it was shown that the cases did not appear to fall into two clearly defined types in accordance with the Ellis (1942) classification, and it was suggested that all the manifestations of nephritis were different expressions of one disease process. The 265 cases will, therefore, all be considered together when assessing the prognosis.

This study was undertaken in the first instance in the course of a clinical trial of an antihistamine drug (mepyramine maleate) in the treatment of nephritis. Initial experience with this drug suggested that it might be of value (Craig, Clark and Chalmers, 1949) and the last 62 consecutive cases of the series reported here were treated with this drug for varying periods. No evidence was obtained that mepyramine maleate influenced the mortality or the duration or severity of the initial illness, nor did it diminish the incidence of cases left with signs of permanent renal damage. This confirms the views of Thomson (1949) and Lawson (1951) based on smaller series of cases followed for relatively short periods. The 62 cases so treated are therefore included with the previous 203 cases for the purpose of the present paper.

Mortality in the Initial Illness

Twenty patients (7·5%) died within one year of the onset of the disease, 16 of them within four weeks. This figure does not, however, represent the mortality to be expected at the present date; 13 of these deaths occurred in the first 100 cases, admitted between 1934 and 1939, and only three in the last 100, admitted between 1945 and 1952. This fall in mortality is largely due to the effects of sulphonamides and antibiotics in controlling antecedent or intercurrent infection. At least seven of the first 13 deaths can be attributed largely to infection (meningitis, septicaemia, pneumonia) with nephritis playing only a secondary role. Of the remaining six deaths, four occurred within three days of admission to hospital, three of them with evidence of circulatory failure. Necropsy in these cases confirmed the diagnosis of nephritis and showed no other cause of death. The three deaths in the last 100 cases were all attributable solely to nephritis.

Long-Term Prognosis

Of the 245 survivors from the initial illness 67 were followed up for less than one year after the onset of their illness and remained untraced at the final follow-up examination. The majority of these cases were considered to have recovered completely when they were last seen, but they will not be further considered here as the follow-up period was so short and the evidence of recovery in some cases incomplete. There remain 178 cases whose present status will now be discussed.

Three cases are known to have died at home, six, eight and 10 years after the onset of their illness, death in each case being certified as due to chronic nephritis. One of these ran a somewhat unusual course in that she had at least 15 distinct relapses with gross haematuria and oedema, many of them necessitating re-admission to hospital; during the remissions between these attacks she was at first relatively well and her blood pressure did not begin to rise until over three years after her first attack. When last seen shortly before her death she had generalized oedema, marked hypertension and gross haematuria but only slight azotaemia.

One hundred and fifty-six cases were examined at a final follow-up examination carried out from one to 13 years after the onset of the illness (in only 13 of them was the interval less than two years). The remaining 19 were unable to attend for examination but were reported to be in normal health. In four cases this statement was supported by the fact that the patient was now overseas, having been accepted in H.M. Forces in the highest physical category and in five others by a report from the family doctor. In 12 of these cases the attack of nephritis had occurred more than eight years previously.

At the final follow-up examination of the 156 cases a record was made of any illnesses suffered since the attack of nephritis, a general physical examination, including blood pressure estimation, was carried out and a single specimen of urine was examined for albumin and by microscopy of the centrifuged deposit. In the case of children admitted between 1935 and 1945 this examination was made in the course of a previous investigation (Russell, 1949); in the remaining children the examination was carried out at the ward follow-up clinic and, in virtually all of these, the results of the final examination were supported by one or more previous examinations carried out at intervals of a few months.

In 115 cases no abnormality was detected at the final examination. In 14 there was evidence of latent nephritis; all these patients had remained clinically well but 10 showed albumin + or + + in the urine, two had a trace of albumin and scanty red cells, one had scanty red cells only and one a trace of albumin and a blood pressure of 120/90 mm. Hg at the age of 8 years.

Eight cases showed evidence of active nephritis. In six of these there was moderate or heavy albuminuria and a history of recurrent episodes of oedema and, in the remaining two, moderate albuminuria and cylindruria and hypertension.

In 19 cases a trace of albumin was found in the urine but the examination was otherwise negative; these cases have been classified as 'uncertain' because of the doubtful significance of this finding in a single non-catheter specimen of urine.

These results are summarized in the following table and it is obvious that they coincide with the majority view on the prognosis of nephritis in childhood.

TABLE

FATE OF 178 CASES TRACED AFTER 1 TO 13 YEARS FROM THE ONSET OF NEPHRITIS

Examined, no abnormality found	115	(75%)
Reported well but not examined	19	
Latent nephritis	14	(8%)
Active nephritis	8	(4%)
Dead	3	(2%)
Uncertain	19	(11%)
	178	

As Snoke (1937) and Payne and Illingworth (1940) maintain that the criteria of cure adopted in the majority of published reports are insufficiently strict to detect latent nephritis, it appeared desirable to investigate some of the cases further and 34 of the

more recent cases were recalled for examination and the performance of Addis counts. (The Addis count technique is described and the range of normal figures defined in the Appendix.) The 34 cases were selected because they were not enuretic and because they lived near enough to attend the hospital without inconvenience and to deliver the Addis count specimens within a few hours of collection. They were unselected in respect of the severity and duration of their initial attack of nephritis and could fairly be considered a representative sample in that respect. They consisted of 24 patients considered healed at the previous examination, four patients considered to have latent nephritis and six who were classified as 'uncertain'.

Counts were performed on one occasion in 12 of the 24 healed cases and on two or more occasions in the remaining twelve. The red cell counts ranged from 0 to 408,000, being lower than 100,000 in 30 specimens. Cast counts between 2,000 and 7,000 were found in four specimens only; no casts were seen in any other specimen. A trace of albumin was found in one specimen only (from a girl); a second specimen from the same child was negative. Addis counts have, therefore, failed to reveal any additional cases of latent disease among these 24 cases passed as healed on routine examination.

In the four cases considered to show evidence of latent nephritis Addis counts gave the following results:

Case No.	Red Cells	Casts	Albumin
A12	360,000	7,000	Trace
A23	2,970,000	0	Trace
A44	760,000	0	Trace
	670,000	7,000	+
	610,000	0	Nil
	200,000	5,000	Trace
	360,000	29,000	+
A49	1,820,000	0	Trace

Except in A12, therefore, Addis counts gave further support to the diagnosis of latent nephritis.

In four of the six cases classed as 'uncertain' Addis counts were normal and the specimens were free from albumin. It appears probable that the trace of albumin found on routine examination in these cases was not significant and that these four cases might also be considered healed.

Of the two remaining cases, A35 had an Addis count of 905,000 red cells and 6,000 casts and the specimen contained albumin+, while A24 had five normal counts during the course of one year (red cells ranged from 87,000 to 208,000 and casts from 0 to 7,000); each specimen contained a trace of albumin, however, and a catheter specimen taken at the time of the last count also showed a trace of albumin. Both cases should probably be classed as latent nephritis despite the succession of normal counts in A24.

Discussion

It is clear, therefore, that Addis counts have modified our views on the final status of these children only in the cases classified as 'uncertain' on routine examination. It appears also from the results quoted from Case A24 that the red cell and cast counts may be repeatedly normal despite persistent slight albuminuria. My impression of the Addis count (based on over 250 counts, personally performed, on these and other cases) is that it is a time-consuming technique with, inevitably, a fairly wide margin of error; it is of value in assessing the doubtful case in which the results of routine examination are equivocal and for certain specific purposes in research in which it may be desirable to have an objective measurement of haematuria; in the practical management of nephritis, however, the information which it gives does not justify the considerable expenditure of time which its routine employment would entail.

If, as seems possible, two-thirds of the 19 cases classified as uncertain are healed, they should at least counterbalance the possibility that some of the 19 cases reported well but not examined have in fact a latent nephritis. This further investigation, therefore, has given no grounds for revising the views summarized in the table on the ultimate outcome of the disease.

The difference between this result and the findings of Payne and Illingworth is difficult to explain. The follow-up period is the same in the two series. Payne and Illingworth recorded the blood pressure and examined the urine on two separate occasions at their follow-up examination; they estimated the amount of albumin in the urine quantitatively and did not perform Addis counts but regarded as pathological more than one red cell per one-sixth field in the centrifuged deposit. They also estimated the blood urea but found this raised in one case only. Their final examination was therefore somewhat more stringent than the final examination of the cases in the present series but not more so than in those 34 cases re-examined and submitted to Addis counts. It would have been reasonable to expect that at least a few additional cases of latent nephritis would be revealed by this further examination in view of their finding of 62 cases of latent disease among 89 cases examined. It is unlikely that selection of cases can account for this discrepancy. The present series includes all children admitted to hospital with nephritis from the North-Eastern Hospital Region of Scotland. The Hospital for

Sick Children, Great Ormond Street, does not draw its cases from any defined area and has always tended to attract unusual or severe cases from a wide area; acute nephritis is, however, an unpredictable disease in which the severity of the early symptoms seems to have little bearing on the long-term prognosis and, while selective admission of severe cases might well result in high mortality figures for the initial illness, it is unlikely to increase to any marked degree the proportion of cases passing into the latent stage. It may well be that there is some foundation for the suggestion made by Snoke (1939) and by Payne and Illingworth that the manifestations of nephritis vary in different parts of the country.

Relation of Initial Symptoms to End-results. An attempt to correlate the end-result with the initial clinical picture in the individual case has proved unrewarding, as in the great majority of previous studies of nephritis. The most that can be said is that of the cases ultimately found to have active or latent nephritis, a higher proportion had a marked hypertension in the initial stages than in the series as a whole. This is of no value in assessing the prognosis in the individual case, however; many cases with severe hypertension have recovered completely. It is probably true that the persistence of hypertension or gross oedema beyond the first few weeks are ominous signs and that cases which still show evidence of nephritis at the end of one year have mostly suffered permanent renal damage. Nevertheless, one case in this series recovered completely though her diastolic pressure never fell below 100 mm. Hg in her first two months in hospital, while another recovered after four separate relapses with frank haematuria, spread over a period of 18 months. In the second case the evidence of recovery is based on three separate examinations at intervals over a period of one year, each examination including a blood urea and blood pressure estimation and an Addis count.

It remains true that to the anxious parents of a child in the early stages of nephritis we can talk only in terms of probabilities and can give no certain opinion on the outcome based on the findings in his particular case.

Summary

An attempt has been made to assess the long-term prognosis of nephritis in childhood by a study of 265 consecutive cases of nephritis admitted to the Royal Aberdeen Hospital for Sick Children over a period of 18 years.

Twenty cases (7·5%) died in the initial illness, but it is shown that the mortality rate has fallen in recent years, largely owing to better control of infection. The mortality to be expected at present is in the neighbourhood of 3%.

The fate of 178 survivors from the initial illness has been assessed from one to 13 years after the onset of the nephritis and 75% appear to have made a complete recovery.

Conflicting views on the prognosis of nephritis are discussed.

A re-examination of 34 cases with the use of Addis counts has shown no evidence of persistent renal damage in cases passed as healed on the strength of routine examination.

No correlation has been found between the initial clinical picture in the individual case and the ultimate result.

APPENDIX

The Addis Count

The sediment count first devised by Addis (1925) has been widely used in America in the follow-up of nephritis and many reports agree on its value in detecting minor degrees of renal damage. So far as I am aware, only Cass (1939) and Giles (1947) have reported the use of this technique in assessing the long-term prognosis of nephritis in childhood in this country.

As originally described by Addis, the count includes the estimation of the protein content and of the total number of red cells, white and epithelial cells and casts in a 12-hour specimen of urine collected after a period of fluid restriction to ensure the production of a concentrated and moderately acid specimen. He suggests that in the female catheterization is essential for accurate counts.

As repeated catheterization is obviously undesirable in children, and as accurate estimations of protein and white cells are of doubtful validity in non-catheter specimens in the female, I have performed only the red cell and cast counts with, in addition, a qualitative test for albumin. There is indeed no clear evidence that the white cell count and albumin estimation provide any additional information of value when the count is used as a measure of activity in nephritis. Lyttle (1933) and Snoke (1938) found that, with urine volumes up to 200 ml. in the 12-hour period, a trace of albumin on qualitative test corresponded to a quantitative result within normal limits. Rubin, Rapoport and Waltz (1942) found that the red cell count showed the most constant and persistent abnormality and considered that, taken alone, it provided a satisfactory index of nephritic activity.

I have followed Addis's original technique in performing the counts with modification of the degree of fluid restriction as suggested for use with children by Giles (1947).

Counts performed on 20 normal children showed a range from 0 to 360,000 red cells and from 0 to 9,500 casts per 12-hour specimen, and I have accepted as the upper limits of normal the figures proposed by Lyttle

(1933), Snoke (1938) and Giles (1947), namely, 600,000 red cells and 10,000 casts.

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DEVELOPMENTAL APHASIA OBSERVED IN A DEPARTMENT OF CHILD PSYCHIATRY

BY

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Recent experience in the Department of Psychological Medicine, Royal Hospital for Sick Children, Edinburgh, has shown that educational difficulties due to developmental aphasia were contributory aetiological factors in a wide variety of behaviour disorders. In the majority of patients the nature of the educational difficulties had not been recognized in time for them to obtain the maximum benefit from remedial teaching. In spite of increasing interest in the condition there still appears to be considerable delay in its diagnosis (Brain, 1955; Methven, 1955; Pearce, 1953; Morley, Court, Miller and Garside, 1955). As a result many children suffer from unnecessarily severe educational retardation and emotional stress. Yet we believe that the histories and findings on examination of the majority of patients constitute a very characteristic clinical syndrome which should be recognized at an early stage. In the present paper we review the findings in 78 children of average intelligence who showed no evidence of cerebral damage.

Terminology

Specific difficulties in reading and writing have long been recognized as occurring in a proportion of children of average intelligence who show no evidence of cerebral damage. The difficulties were attributed to 'word blindness' by Morgan (1896) and Kerr (1897). When it became realized that many of the children with difficulties in reading and writing also had difficulties in comprehending and using the spoken word the terms 'developmental aphasia' and 'developmental dysphasia' were coined to describe this syndrome (Hinshelwood, 1917; Orton, 1937). Both terms are unfortunate and liable to lead to confusion, for though the majority of patients with developmental aphasia do show expressive or receptive aphasia the difficulties in reading and writing are more consistently present manifestations. The term developmental aphasia has, however, been retained in this paper for want of another more suitable.

To designate the reading and writing difficulties the terms dyslexia and dysgraphia are employed. By dyslexia is meant specific difficulty in learning to read. This is evidenced quantitatively by retardation in reading attainment relative to the best available estimate of intelligence and qualitatively by resistance to normal methods of teaching and the recurrence of certain characteristic forms of error. The term dysgraphia applies similarly to the operation of writing. The quantitative assessment of dysgraphia is by a test of spelling, but the qualitative assessment covers all aspects of the writing operation, of which motor function is only a part.

Selection of Patients

Eight hundred and four patients were referred to the Department from January, 1954, to July, 1955, for a wide variety of symptoms, which are shown in Table 1. Among them were 250 in whom educational maladjustment was thought to be important, though only a minority were referred with the complaint of being backward at school. In most of the children educational maladjustment was attributed to intellectual or personality defects or to neurological, visual or auditory abnormalities.

There were, however, 78 children who proved to be of average intelligence on test and who were diagnosed as suffering from developmental aphasia. None of them showed evidence of neural, auditory or cerebral abnormalities to which their symptoms could be attributed.

Sex and Age Distribution

Sixty-five of the patients were boys, and 13 were girls. The ages varied from 6 to 15, but more than half were between the ages of 6 and 9 years.

Reasons for Referral

The reasons given for the referral of the patients suffering from developmental aphasia, and those of other children sent to the clinic, are shown in Table 1.

TABLE 1
CAUSES OF REFERRAL

	Primary Causes of Referral		Secondary Causes of Referral	
	Approximate % Series of 78 Patients	Approximate % 726 Other Clinic Patients	Approximate % Series of 78 Patients	Approximate % 726 Other Clinic Patients
Educational difficulties with or without other symptoms	33	20	39	4
Speech defects or retarded speech	5	6	9	2
Withdrawal, *e.g.*, day-dreaming, solitariness, failure to make friends, immature behaviour	12	17	9	8
Night terrors	6	5	12	2
Aggression	3	2	6	8
Thumb-sucking and clothes chewing, etc.	3	1	8	5
Blinking, twitching, habit spasms	5	3	5	5
Temper tantrums	4	5	8	7
Aches and pains	4	4	8	6
Enuresis	6	11	10	10
Encopresis	4	4	4	6
Asthma	5	2	1	2
Truanting	4	3	6	1
Stealing—pilfering	6	10	3	7
Other	0	7	0	4
Total	100	100	—	—

It will be observed that educational difficulties (sometimes specified further as poor progress in learning to read and write) were the premier cause in 33% of the cases. They were the only symptom in 19%, and associated with others in 14%. In a further 39% they were a secondary cause, but in as many as 28% learning difficulties were not mentioned at the time the initial history was taken. Apart from a higher proportion of patients referred on account of learning difficulties, the causes of referral of the group studied were remarkably similar to those of other clinic patients who did not suffer from developmental aphasia.

The Method of Study

The patients suffering from developmental aphasia were studied in more detail with the aim of defining more accurately the difficulties from which they suffered, and the extent to which hereditary, social and educational circumstances seemed important in producing them.

History Taking. Psychiatric social workers in the Department took detailed histories of the child's physical, mental and social development, and noted any family history suggesting psychiatric disturbances or hereditary physical disorders. Teachers were asked to supplement these histories with details of the child's educational progress. The handedness of the patient's siblings, parents and parents' siblings was determined, usually of necessity by questionnaire. On the basis of their histories the psychiatric social workers attempted to define some of the aetiological factors which might be important in the patient's educational or general behaviour symptoms.

Physical Examination. Every patient was subjected to physical examination, including detailed neurological examination. Audiometry, detailed ophthalmic investigation and electroencephalography were performed when they seemed indicated to exclude the possibility of sensory or cerebral abnormalities.

Tests of 'Handedness'. Handedness was tested rather unscientifically by noting the hand which the child used in each of four performance tests carried out three times. Each patient was asked to turn a door handle, dig with a trowel and catch a ball. Patients using each hand six times or one hand seven times and the other five in the total of 12 sub-tests were arbitrarily classified as ambidextrous (A). Patients using one hand eight or nine times and the other three or four times were classified as being ambidextrous with lateralizing preference (A/L or A/R). If the child used one hand, 10, 11 or 12 times, as the majority of other clinic children did, they were classified as showing definite hand preference (R or L). 'Footedness' was tested by standing the child at the bottom of a flight of stairs without a banister, and making him climb them three times, and asking him to kick a ball three times. 'Eyedness' was tested by asking the patient to look through a punch hole in a card attached to the desk three times, and to sight a gun or a telescope three times. The eye and foot used for each test was noted. If the patient used each foot or eye for three sub-tests he was classified as showing no preference (A). If he used one eye or foot for four sub-tests he was classified as showing slight preference (A/R or A/L) and if he used the same side in five or six sub-tests he was considered to show marked preference (R or L).

Speech. In as many cases as possible, interviews with patients were recorded on tape, in order that

detailed study of their speech could subsequently be made in collaboration with phoneticians. In a few cases it was found impossible to make recordings and speech studies were necessarily incomplete.

Apart from the recording of conversation, receptive and expressive aphasia was also tested by means of a short series of selected questions and commands.

Psychiatric Assessment. Psychiatric interviews with the patients were as frequent as possible and an attempt was made to find out what environmental factors the child felt to be important in causing his difficulties. The final psychiatric assessment was made only after several interviews and in the light of the social history, family background and educational and psychological assessments.

Psychological Assessment. A formal assessment was made of the intellectual capabilities and educational attainment of every patient, excluding 13 who were found to be too anxious or too severely affected for the results to be of value. In 13 of the earlier patients to be studied the Terman Merrill test form L was used in conjunction with the performance scale of the Wechsler intelligence scale for children as a test of intelligence. In the remaining 52 patients complete results are available from testing in the Wechsler scale (hereafter referred to as WISC), and only these will be formally analysed, as it is not legitimate to combine intelligence quotients (I.Q.s) from different tests.

The results of the intelligence test were not taken as exhaustive indications of intellectual capacity. The limitations inherent in them and the degree to which the results are affected by anxiety or specific difficulties are recognized, but the tests were used as the best available estimate of the level which the child might be expected to reach in the basic skills of reading and writing.

NATURE OF THE TESTS. The WISC consists of two scales, or sets of sub-tests, named the verbal and the performance scales. The verbal scale contains five sub-tests:

(1) Information, a test of general knowledge; (2) comprehension, a test of the ability to form and express simple judgments; (3) mental arithmetic, a test of problem solving rather than calculating; (4) similarities, a test of the ability to categorize, and express this in words; (5) vocabulary, a test of the ability to define, or give verbal equivalents for given words.

The performance scale also has five sub-tests:

(1) Picture completion, a test where the child has to find what is missing in a pictured object: perception and visualizing power enter into this. (2) Picture arrangement, in which a series of pictures has to be arranged in correct order to tell a story. (3) Block design, a version of Kohs' Blocks, where geometrical designs have to be reproduced to correspond with a given model. (4) Object assembly, a test where cut-up silhouettes of objects bearing some single line drawing have to be put together. Both outline and line drawing are used as clues, and all the joins are straight line cuts. (5) Coding test, a series of geometrical shapes have to be inserted underneath their appropriate numbers (1-9) according to a code given at the top of the page. The version for children under 8 is similar, but does not involve numbers at all.

EDUCATIONAL ASSESSMENT. The educational attainment in reading and writing of each child was assessed quantitatively by using the Schonell graded word list as a reading test, and the Schonell graded spelling list A as a spelling test. From the scores obtained by each child are calculated his reading and spelling ages. From these are derived his reading and spelling quotients by reference to his chronological age. Tests for letter and word reversal were also given and samples were obtained where possible of the child's reading and writing of continuous meaningful material.

Results of Investigation

Family and Social Backgrounds. The place of all the legitimate children in the family was noted in every case. The distribution by place in the family was not found to differ significantly from that shown by the Registrar-General for Scotland, 1951, for all legitimate live births in Scotland.

The distribution by social class of the father of children with developmental aphasia was compared to that of legitimate live births in counties or cities in Scotland in 1951. There is a significantly higher proportion of patients in social classes I and II, and a smaller proportion in social classes IV and V.

Seventeen of the 78 patients, or 22%, came from broken homes. In 10 cases the parents were divorced or otherwise separated. There was marked parental disharmony, to the point of intermittent separation in the majority, in another 15 cases. Five children were adopted and five lived in institutions or with foster parents. Fifteen of the patients in intact homes had a history of more than one month's separation from the parents in the first two years of life.

One or both parents had received psychiatric treatment in 16 cases, and in a further 13 one or both parents were thought by the psychiatric social

TABLE 2
HANDEDNESS, EYEDNESS AND FOOTEDNESS OF 78 PATIENTS WITH DEVELOPMENTAL APHASIA

	R		A/R		A		A/L		L	
	Number	Approximate %	Number	Approximate %	Number	Approximate %	Number	Approximate %	Number	Approximate %
Handedness ..	13	17	28	35	14	18	14	18	9	12
Eyedness	10	13	7	9	8	10	12	16	41	52
Footedness ..	18	23	16	21	15	19	12	16	17	21

R = right preference; L = left preference; A = no preference; A/R and A/L = slight preference.

worker and psychiatrist in the clinic to be in need of it. A total of 36 of the 149 parents about whom information was available, or 24%, had had or were considered to have need of psychiatric help. Anxiety neurosis was diagnosed in 24, obsessional neurosis in three, psychosis in five and other disturbances in four. At least 18 of the patients had siblings who had been referred to child guidance or psychiatric clinics.

The parents of 38 children were felt to be unduly concerned about and ambitious for their children's educational attainment. In the majority of these the parents' own anxiety had been projected to the children, whose fear of failure and of letting their parents down was very marked. In at least three cases night terrors could be directly related to the fact that parents had laid undue stress on educational achievement and their children feared that their failure at school might lead to parental rejection. These fears were especially liable to occur in children who had been adopted or who came from broken homes. Typical examples of placing too much stress upon educational achievement may be cited.

The owner of a fish and chip shop who had always had an ambition to be a doctor or a lawyer, and who had quarrelled with his wife and the elder of his two sons, was very ambitious vicariously for the younger, who was of no more than average intelligence. The mother had rejected the boy since birth but the father sent him to an expensive boarding school, which he could ill afford. The son's dyslexia and dysgraphia soon retarded his progress at school. He was referred to the clinic in a state of acute anxiety at the age of 9, very aware of his failure and very fearful that his father's disappointment would lead to rejection by him as well as by the mother.

The only adopted child of brilliant University honours graduates was referred to the clinic at the age of 10 on account of day dreaming, solitariness, a tendency to burst into tears and irrational fears. Investigation showed that he was of no more than average intelligence and was suffering from severe dyslexia and dysgraphia. He had fallen a year behind at school in spite of the fact that he had received several hours of exhausting and often ill-tempered coaching from his parents each night. He felt despised by them and inferior to his contemporaries, and was desperately afraid of parental rejection.

Laterality. The distribution of handedness, eyedness and footedness as determined by the tests described on page 162 is shown in Table 2. It will be observed that 14, or approximately 18% of the patients, were considered to be predominantly ambidextrous showing no obvious hand preference on test. A further 42 showed only slight preference. Nine were left-handed and 13 right-handed. A very high proportion of patients, 52%, were found to be left-eyed and 21% were left-footed.

As a result of questioning parents about the handedness of other members of the families, it was found that 65 of 108 parents, or 59%, were right-handed, 11% left-handed and 30% ambidextrous. Of the 98 siblings about whom information was obtained, 63% were right-handed, 18% were left-handed and 19% were ambidextrous. Information was obtained about 112 siblings of the parents. Eighty-four per cent. were right-handed, 5% left-handed, and 9% were stated to be ambidextrous. It should be emphasized, however, that these figures were not obtained by direct testing and much reliance cannot be placed upon them.

Twinning. Information was sought as to the number of twins in the families of patients with developmental aphasia. Of the 78 patients, six were known to be twins, including one pair, approximately 8%. Six of the 108 parents about whom details were obtained, were one of twins, and seven of the 112 uncles and aunts of patients were twins, including two pairs. Of the 98 siblings of the patients, four were single survivors of twin births, and two others were a surviving pair.

Speech Defects. A study of the recordings taken during the psychiatric interviews was found to be essential for the detailed study of the abnormalities of speech shown by patients with developmental aphasia. Dysarthria was encountered in only five patients in the sense in which the term is used by Morley, Court and Miller (1954). On the other hand articulatory apraxia was extremely common and occurred in 40 cases. Its commonest manifestations consisted in distortions of speech sounds,

TABLE 3
AGES AT WHICH 78 PATIENTS WITH DEVELOPMENTAL APHASIA WALKED AND TALKED

Age in Months	Number of Cases			Percentage of Known Cases		
	Walking	First Words	Phrases	Walking	First Words	Phrases
9–12	17	2	0	23	3	0
12–15	36	17	0	49	23	0
15–18	17	12	0	24	16	0
18–24	3	17	0	4	23	0
24–30	0	15	14	0	19	20
30–36	0	5	20	0	8	29
36–42	0	5	13	0	8	19
42–48	0	0	12	0	0	18
48+	0	0	9	0	0	14
Unknown	5	5	10	—	—	—
Total	78	78	78	100	100	100

substitutions of one sound for another, irregularities of rhythm, and, in very severe cases only, disturbances in intonation. In children with only slight defects of speech, defective sound production was usually the only abnormality. In more severe cases it was accompanied by disturbances of rhythm which could be very marked. These appeared to be due most commonly to faulty synchronization of abdominal and chest pulses. Abrupt pauses in the middle of phrases were usually due to a dysrhythmic chest pulse and were sometimes accompanied by abrupt glottal closure. Less abrupt pauses were due to expressive aphasia in some cases and in others to unknown causes. Because of the rhythmic disturbance and the tendency for sounds to be slightly distorted the speech tended to sound rather monotonous in some patients though closer study revealed intonation to be normal in the majority. At first hearing the recordings showing marked rhythmic disturbance gave an impression of disordered melody of speech, or dysprosody, as described by Monrad-Krohn (1947). Occasionally when a child with expressive aphasia reversed the order of words in a phrase very anomalous intonation could result. Stutter was evident in seven cases.

In general the severity of speech defects in any single case appeared to be in direct proportion to the severity of the retardation of its development. They were more marked in younger children, and those with expressive or receptive aphasia.

Expressive and Receptive Aphasia. Though the motor milestones of the patients were within normal limits speech development was retarded in more than half the children in the series (Table 3). Forty-two of the patients, or 58%, said their first words after 18 months, 25, or 35%, after 2 years, and five, or 8%, were over the age of 3. The ability to construct phrases was also delayed. Twenty-one, or 32%, could make phrases only after the age of 3½ years, and nine, or 14%, were over 4 years. In all the 42 patients whose first words came after 18 months and in a proportion of those who spoke earlier, pronunciation remained grossly defective for a prolonged period and some were still incomprehensible to everyone but the parents at the age of 4 or 5.

By this time it was evident that the majority of these children had specific difficulties in comprehending speech and in finding words with which to express themselves. Parents often found that the children could talk freely when playing at ease, but that they could not do so when under emotional stress. Fifteen had been noted to blurt out words or phrases which were inappropriate in meaning to what they wanted to say and 12 reversed the order of words in phrases repeatedly without correcting themselves. A commoner complaint occurring in 26 children was typically described as, 'He keeps on forgetting the names of things and then has to describe them by waving his arms about.'

Difficulties in perceiving the significance of speech were suggested by parents complaining that their children were deaf or disobedient, that they ignored what was said to them, or that it took a minute or two before they could answer questions or obey commands.

The most frequent manifestations of aphasia were use of the wrong word (paraphrasia), inability to recall the names of people and objects (nominal aphasia), sudden hesitation during speech because of failure to find words for what the child wanted to express and alterations of the word order which frequently made nonsense of phrases which should have been meaningful. Perseveration was encountered occasionally, and a few severely affected patients were found who were incapable of comprehensible speech except when completely relaxed. Typical examples of the common forms taken by these disorders in practice may be cited. A 9-year-old boy admiring a toy gun said, 'It's a fired one, it isn't, it isn't, it isn't, it's a fired one it

can . . .' instead of 'It's a fine one, isn't it? It can fire'. Another child was asked the name of his teacher after an excited conversation about cowboys, and answered, 'Roy Rogers, Sir, Rogers, Sir, Sir, not Rogers . . . not sir, Macmillan'. The 'hangover' from preceding conversations was often evident in the content of phrases with which these children had especial difficulty.

Receptive aphasia was manifest in an apparent inability to answer abrupt questions or commands at once unless they were accompanied by gesture. When asked to put out his tongue, or shut his eyes, for example, the child would find it very difficult to comprehend at once what was asked, but would imitate the action of the examiner at once. It was found that unnecessarily detailed descriptions of objects and of actions were rewarded by more rapid and accurate comprehension than were simple statements. Thus a request to, 'Turn the small, round brown handle of the large cream-painted cupboard door and then open it', was much more easily comprehended than a simple request to, 'Open the cupboard'. It was found that under stress and being made to hurry the majority of children with receptive aphasia had difficulty in picking out objects from pictures when these were named to them. It was typical of the children with receptive aphasia that they showed the habit of asking that everything which was said to them be repeated, almost by reflex action. The habit of saying 'What', 'Beg pardon' to everything said by teachers had resulted in strappings for impertinence in a number of cases. The effect of stress appeared to be more marked in accentuating the symptom of receptive aphasia than of expressive aphasia, dyslexia or dysgraphia. When aphasia was present only under exceptional emotional stress or on testing it was classified as mild. When it resulted in intermittent failure to comprehend what was said, or to find appropriate verbal expression, it was classified as moderately severe and when it resulted in persistent difficulty in comprehension and expression it was considered to be severe.

Behaviour and Personality Disturbances. Within six to 12 months of starting school the majority of patients with developmental aphasia had shown symptoms of anxiety, expressed in either behaviour or personality disorder. As has been indicated by the causes of referral, the symptoms shown varied greatly in type and in severity according to the child's personality, and his social and educational environment. Some children reacted aggressively by bullying their fellows, others attempted to compensate for their failure by becoming class clowns and spent their time amusing their fellows and infuriating their teachers rather than attempting work which was becoming progressively more difficult or impossible. One intelligent boy of 14 with severe dysgraphia and dyslexia reacted vigorously to being strapped for spelling mistakes by housebreaking and stealing. But the housebreaking was confined to the school, and the stealing was only from the spelling teacher.

Other children attempted to withdraw from the stressful situation. More than four weeks' absence from school each year on average was reported by 13 cases. In three asthmatics there was a clear relationship in time between attacks and the occurrence of exams or other educational strains at school. Straightforward truanting was present in eight cases. A more subtle character produced vomiting when his work was beyond him, as often as three or four times a week, until his teachers ceased to send him home when he did so.

Children with less robust personalities tended to react to the educational stress less directly. At least two of the five children with nocturnal enuresis had been dry until six months after starting school and were only wet when their schools were in session. Day dreaming, tearfulness, solitariness and temper tantrums were also frequently mentioned in the histories.

As might be expected, the degree of anxiety found bore little relationship to the severity of the dyslexia, dysgraphia or aphasia. Social environment, intelligence level and constitution were more important determining factors.

Psychological and Educational Assessment. The following figures were available for each of the 52 children fully tested: Verbal I.Q., performance I.Q., composite I.Q., reading quotient (R.Q.) and spelling quotient (S.Q.). The 52 children had a mean verbal I.Q. of 101·42, a mean performance I.Q. of 96·1, a mean composite I.Q. of 98·15, a mean R.Q. of 89·0 and a mean S.Q. of 78·6. The difference between verbal and performance I.Q.s was not significant at point 0·05 level. The group as a whole was, however, markedly retarded in reading and more so in writing, the discrepancies being 9·15 points and 19·55 points respectively. Merely to state the results in this way, however, obscures certain important variations in performance, and to demonstrate these the children were subdivided into three groups (Table 4).

Results of Psychological Assessment. In group (*a*) the verbal scores were higher by more than 8 points than the performance scores, in group (*c*) the

TABLE 4

COMPARISON OF READING AND SPELLING QUOTIENTS OF PATIENTS BY RELATIVE SCORES ON PERFORMANCE AND VERBAL SCALES OF THE WECHSLER TEST FOR CHILDREN

Group	Definition	Number I.Q.	Verbal I.Q.	Performance I.Q.	Composite I.Q.	Reading Quotient	Spelling Quotient
(*a*)	Verbal score better than performance	23	112·3	91·5	101·7	100·3	91·5
(*b*)	Verbal and performance equivalent	16	95·6	95·1	95·3	83·5	71
(*c*)	Performance better than verbal score	13	89·3	105·6	97·45	76·4	65

performance scores were higher by more than 8 points than the verbal and in group (*b*) the scores were equivalent, not varying by more than 8 points. The reading and spelling quotients (R.Q. and S.Q.) for each group are also shown. The differences in the composite I.Q.s of the three groups are not significant.

A detailed statistical investigation of the sub-test scores on the WISC, studied in relation to severity of retardation and of aphasic symptoms, is at present being undertaken. Results so far obtained appear to indicate that the two sub-tests most difficult for the whole group were similarities and digit symbol, and that the tests differentiating most markedly between groups (*a*) (verbal better than performance) and (*c*) (performance better than verbal) were comprehension and vocabulary.

In the course of administering the tests to the patients several characteristic types of confusion were observed repeatedly. In the performance tests, failure to analyse and synthesise patterns, inability to distinguish a pattern from its mirror image and reversal of normal left-to-right serial order were frequent. In the verbal tests confusions similar to those described on page 165 were common. Contrary to what one might expect, examples of these occurred even in records where the final numerical score was relatively high (Table 5).

TABLE 5

SEVERITY OF DYSLEXIA AND DYSGRAPHIA BY RELATIVE SCORES ON VERBAL AND PERFORMANCE TESTING ON THE WECHSLER SCALES

Group	Dyslexia			Dysgraphia		
	Mild	Moderate	Severe	Mild	Moderate	Severe
(*a*)	16	6	1	7	7	9
(*b*)	5	5	6	2	5	10
(*c*)	1	4	7	2	3	8

The relative severity of dyslexia and dysgraphia, as shown by R.Q. and S.Q., was measured by calculating the difference between the composite I.Q. and the R.Q. and S.Q. in each case. Where the discrepancy was less than 10 points, dyslexia or dysgraphia was considered to be mild, when less than 20 points it was considered moderately severe and when it was 20 points or more it was considered severe. In Tables 5 and 6 are shown the distributions of mild, moderately severe and severe cases of dyslexia and dysgraphia by relative scores on the Wechsler performance and verbal scales, and by the presence or absence of aphasia. There are more severe cases in group (*b*) than in (*a*), and most in (*c*), and there are more among the aphasic than the non-aphasic patients.

TABLE 6

DISTRIBUTION OF APHASIC PATIENTS BY RELATIVE SCORES ON VERBAL AND PERFORMANCE TESTING ON THE WECHSLER SCALES

Group	(*a*)	(*b*)	(*c*)	Total
Patients without expressive aphasia ..	10	3	1	14
Patients with expressive aphasia ..	13	13	12	38
Total	23	16	13	52

Analysis of Errors. The reading errors made by the 52 patients at the time of educational assessment were classified though this was rendered difficult by the fact that similar misreadings may be due to a variety of different mistakes. Most of the reading errors have counterparts in the writing errors which the patients also showed (Table 7).

Though all the various reading errors were encountered in all three groups, (*a*), (*b*) and (*c*), the frequency of each individual type varied. Omission of words and reversal of word order (Error 4) were equally frequent in all groups. Confusion of sounds and symbols, inability to synthesise words from their constituent sounds and failure to recognize the meaning of words when sounded (Errors 6, 7 and 8) were more frequent in groups (*b*) and (*c*) than in group (*a*). On the other hand groups (*a*) and (*b*) showed mistakes in 'mirror-image' letters and a tendency to guess at words more frequently (Errors 1 and 5) than did group (*c*) (Table 8).

Treatment. Treatment had three aspects. From the psychiatric point of view the aim was to diminish the patient's anxiety and restore his lost confidence. The majority of patients responded well once the

TABLE 7
READING AND WRITING ERRORS IN PATIENTS WITH DEVELOPMENTAL APHASIA

Reading Errors	Writing Errors
1. Mistaking one letter for another, especially for its mirror-image, b for d, p for q or g, leading to misreading of words	Writing one letter for another, especially its mirror-image, and writing distorted letters
2. Altering the letter order in a word, or part of a word, often reading backwards, pot for top, its for sit	Confusing the order of letters or groups of letters in a word, especially tending to reverse them
3. Repeating the first letter or group of letters at the end of the word, gag for gas	Repeating the initial letter or group of letters at the end of the word
4. Omitting small words, and reversing word order when reading prose	Omitting small words, especially prepositions
5. Inability to take in the whole word pattern, and guessing at the word from the first or last letters or from the context	Inability to recall visual word patterns, and tendency to resort to phonic spelling, *i.e.*, guessing from analogies of sounds
6. Confusing the sounds belonging to the written symbols, *e.g.*, sounding sit as r-u-p. This may lead to neologisms.	Inability to connect the correctly analysed sounds of the word with the appropriate written symbol
7. Inability to synthesise sound units into meaningful words, or to synthesise the sounds in the correct order, though the units are correctly sounded. (The child spells out p-o-t, but cannot produce the word pot—spells out s-i-t, and says its.)	Inability to analyse the word into its constituent sound units or to retain these in the correct order
8. Inability to recognize the meaning of a word or a phrase, though it may be correctly sounded and synthesized	Syntactical and other confusions in connected material indicative of inability to perceive the meaning of what is to be written

TABLE 8
PERCENTAGE DISTRIBUTION OF WORD AND LETTER REVERSALS IN 52 FULLY TESTED PATIENTS

Group	(*a*)	(*b*)	(*c*)
Letter reversals (errors type 1) ..	56·5	81·2	30·0
Word reversals (errors type 2 and 3)	26·1	31·2	38·8

nature of their educational disabilities was explained to them. From the social point of view the aim was to minimize the environmental stresses to which the child was exposed, particularly by modifying the parental attitude to education when this was resulting in too much pressure being exerted on him to be a brilliant scholar. At the same time teachers were encouraged to take a sympathetic attitude to the child's educational handicaps, and a change of school was recommended in severe cases if this was not forthcoming.

From the educational point of view the child was encouraged to appreciate the shapes and patterns of words by using his proprioceptive apparatus. By teaching writing and reading in close association, proprioceptive and visual appreciation of word and letter shapes was encouraged simultaneously, and reading and writing tended to improve together. The rather experimental teaching methods used will be discussed in more detail in a later paper.

Discussion

Reversals of letters and of letter order occur in a very large proportion of normal school children for a few weeks when they first begin to read and write. As long ago as 1896, however, persistent difficulty in perceiving the significance of written material was noted to occur in a proportion of otherwise normal children without evidence of cerebral damage (Kerr, 1897; Morgan, 1896). To these difficulties the descriptive term 'word blindness' was applied. Initially, difficulties with reading appear to have been regarded as the sole manifestation of the disorder, and only gradually have other clinical features come to be added to comprise the syndrome of developmental aphasia (Hinshelwood, 1917; Orton, 1937; Ombredane, 1944; Hallgren, 1950; Morley *et al.*, 1955). It is now generally recognized that specific dyslexia is almost always associated with specific dysgraphia, and the frequency with which receptive aphasia (congenital auditory imperception) and expressive aphasia (verbal dysphasia) occur is also being realized (Brain, 1945, 1955).

The Aetiology of Developmental Aphasia. In a proportion of patients with dyslexia, dysgraphia and aphasia it is by no means easy to determine whether the symptoms are the result of cerebral damage or malformation, or due to developmental aphasia (Dunsdon, 1952). In the present series great care was taken to exclude cases with cerebral damage by detailed examination and investigation. None had a history suggestive of cerebral birth injury and no significant neurological abnormalities were apparent.

There is, in fact, much evidence that there is a hereditary element in the aetiology of developmental aphasia. As a result of a detailed study of dyslexic patients and their families, Hallgren obtained evidence suggesting that dyslexia was due to an autosomal Mendelian dominant gene. If this is so the penetrance of the gene must be extremely variable and probably depends upon a number of complex environmental factors, for the severity of the symptoms shown even by identical twins varies very greatly.

Though the majority of published series of dyslexic patients report a high preponderance of males over

females, in about the ratio of 5 to 1, the explanation for this is obscure (Wallin, 1921, 1949). Our male to female ratio of 5 to 1 in the series compares with that of 5·5 to 4·5 for all other clinic referrals. Hallgren states that he could find no evidence of sex linkage in the inheritance of dyslexia. In part the difference may be due to selection of cases. In series consisting of referrals to child guidance clinics the male preponderance is greater than in series derived from field studies. It seems possible that the patriarchal societies of both Sweden and Scotland place greater emphasis on the need for educational success in the male than in the female and that this results in readier referral of the male who is having learning difficulties.

The sex difference may be related to the fact that there are more ambidextrous males than females in the population and that aphasic symptoms occur more frequently in children with slight tendencies to hand and eye preference than those with marked unilateral dominance (Granjon-Galifret and Ajuriaguerra, 1951).

It has been suggested that dyslexia and dysgraphia tend to occur more frequently in children with a family history of twinning, and in twins than in those who are single births (Macmeeken, 1939). In the present series it was found that there was a high proportion of twins amongst the patients, their siblings, parents and their uncles and aunts compared to that expected on the basis of the estimate that 1·3% of all live births are twin. The place in the family of patients with developmental aphasia is not significantly different from that of all live births in the general population in Scotland (Registrar General for Scotland, 1951). This is in accordance with the findings of Hallgren in Stockholm.

That environmental factors play an important factor in exacerbating aphasic symptoms is indicated by the way in which many of the patients showed dramatic improvement in school work when home and school conditions were ameliorated. The high proportion of patients in social classes I and II is probably due in part to the greater stress laid by parents and schools on the need for educational success than in the lower social classes. The frequency with which a history of broken homes, parental disharmony, parental over-anxiety and prolonged periods of separation from parents in the early years of life was found has been described.

All these factors might be regarded as environmental causes of anxiety and insecurity in the child and thus as contributory factors in his lack of confidence and poor educational progress.

Handedness of Patients with Congenital Aphasia and of their Families. The handedness, eyedness, footedness and 'visual-fieldedness' of children suffering from dyslexia and dysgraphia have attracted much attention, but there is still great controversy about the significance of finding evidence of sinistrality, crossed laterality between hand and eye and ambidexterity.

In a series of elementary school children in Edinburgh it was found that dyslexia was commoner amongst those who were left-eyed than those who were right-eyed (Macmeeken, 1939). The possible aetiological importance in dyslexia of sinistrality, crossed laterality and ambidexterity has been stressed by Orton (1937) and by Schonell (1948). It has been suggested, however, that the laterality of visual-fieldedness is of greater importance in determining the side of cerebral dominance than is the laterality of eyedness. Unfortunately the apparatus used for testing fieldedness is impractical for routine clinical use and the method is not without theoretical objections (McFie, 1952).

No significant relationship between the incidence of left handedness, left eyedness or cross laterality and the occurrence of congenital dyslexia was found in a controlled study by Hallgren (1950). Exception must be taken, however, to his tendency to classify patients as either right or left handed rather than as ambidextrous as was done by Granjon-Galifret and Ajuriaguerra (1951). The latter authors attempted to define handedness and eyedness in terms of the strength of the lateralizing propensities found on test. They reported that there was a higher incidence of ambidexterity, absence of strong hand preference, in a series of dyslexic patients than in a series of controls. There was no significant difference in the incidence of left handedness between the two groups.

It will be seen from Table 2 that in our series 56 of the 78 patients, or approximately 71%, failed to show marked preference for one hand, and 56% showed little preference for one foot rather than the other. Thirty-five per cent. of patients were considered to show marked laterality in eyedness though as many as 52% were left eyed on test. When handedness is defined in terms of absence of marked laterality it is obviously of little value to determine the numbers of patients showing crossed laterality of dominant hand and eye. Our findings are very similar to those of Granjon-Galifret and Ajuriaguerra in their group of dyslexic patients allowing for difference in classification and our cruder techniques of determining laterality.

A number of authors have reported that there is a high incidence of left-handedness and ambi-

dexterity amongst relatives of children with dyslexia (Orton, 1937, 1943). That this is so has been denied by Hallgren (1950). In an unselected series of 4,449 elementary school children in Edinburgh under the age of 9 years who were examined by questionnaire, it was found that 8·65% were left-handed with a significantly higher number of boys than girls (Chisholm, 1954). This percentage is lower than that for patients (11%), their siblings (18%) and their parents (11%) in our series of cases. But these differences are not statistically significant. Series of normal children with which to compare the incidence of ambidexterity in our patients are not available.

Description of the Symptoms. The difficulties in learning to read and write have been fully described by a number of authors whose work is summarized by Hallgren (1950) and Brain (1955). They are very similar to those encountered in our patients. We have found no author, however, who sufficiently stresses how often retarded speech development, expressive and receptive aphasia and speech defects are found among patients with dyslexia and dysgraphia. The association of these disorders is noted by a number of workers, but there still appears to be a tendency to consider dyslexia and dysgraphia on the one hand, and expressive and receptive aphasia on the other, as rather distinct disorders (Orton, 1937; Brain, 1955). Since our series is not dissimilar in other respects to a number of others which have been published our higher incidence of aphasia is unlikely to be due to differences in sampling.

The speech defects which were noted in our cases were very similar to those described by Morley *et al.* (1955). Unfortunately most of their patients were under school age and the incidence of dysgraphia and dyslexia amongst them could not be determined. It seems likely, however, that these disorders must occur relatively commonly amongst similar patients referred to clinics of speech therapy.

A number of authors have stressed the importance of emotional factors in determining educational difficulties in general and reading difficulties in particular (Burt, 1947; Gann, 1945). On the other hand the complex relationship between anxiety provoked by school difficulties and dyslexia and dysgraphia exacerbated by anxiety has not received the attention it deserves, though emphasized by Orton (1937) and Hallgren (1950). The latter author found that 58% of a series of dyslexic patients ascertained in school had one or more nervous symptoms compared with 33% in a control group. The symptoms shown by our cases were not dissimilar from those of other referrals for child guidance.

Four common types of emotional disturbance secondary to specific dyslexia—the 'couldn't care less', the paranoid reaction to the teacher, marked feelings of inferiority and a tendency to emotional blocking—were described by McCreedy (1926). We would only comment that the 'couldn't care less' attitude is very often a shallow veneer on the surface of deep anxiety, that in Scotland, where the strap is used too freely to encourage learning, the paranoia is usually justified, that the feelings of inferiority are often associated with fears of rejection and that it was often extremely difficult to determine to what extent 'blocking' was emotional and how much of it was due to aphasia.

Nature of the Disability in Congenital Dyslexia and Dysgraphia. Many efforts have been made to specify more precisely the nature of the difficulties in reading and writing suffered by dyslexic and dysgraphic children. Unfortunately these have been expressed in a variety of incomprehensible and mutually incompatible terms which make appreciation of their merits very difficult, as has been noted by Schilder (1944) and Brain (1955). They vary from interpretations of the symptoms in terms of defective *Gestalt* and theories of abnormal functional cerebral symmetry to logical positivist reflections upon individual variations as to what is understood by single words. The relevant theories and literature have recently been reviewed by Brain (1955).

A study of the test results in Table 5, in which the degrees of dyslexia and dysgraphia for the three groups are shown, yields the following observations:

(1) The groups increase in severity of retardation relative to composite I.Q., the increase being steeper in writing than in reading.

(2) The increase in severity of both dyslexia and dysgraphia is directly proportional to the verbal I.Q., the R.Q. being approximately 12 points below the verbal I.Q. in each group, and the S.Q. being from 21 to 24 points below.

(3) In each group dysgraphia is more severe than dyslexia.

(4) Group (*c*), which has the highest mean performance I.Q., is the most severely retarded.

As indicated above in intelligence testing, group (*a*) showed predominantly spatial difficulties, group (*b*) showed spatial and aphasic verbal difficulties in equal proportions, while group (*c*) showed predominantly aphasic difficulties. It was also noted that there seemed to be characteristic errors associated with these groups, certain kinds being more typical of groups (*a*) and (*b*), and certain others of groups (*b*) and (*c*).

Group (*a*), in which the proportion of aphasic

patients was small, was relatively free of errors involving the sound of individual letter symbols, the synthesis of sounds into words and the comprehension of words or phrases when sounded and synthesized (Errors 6, 7 and 8). Their mistakes were chiefly in perceiving or recalling shape and position (Errors 1, 4 and 5) and formed a parallel to their failures in intellectual testing. Group (*b*) exhibited similar errors, but in addition showed many errors in common with group (*c*). Both these groups, but (*c*) especially, contained patients with receptive and expressive aphasia, and their errors consisted mainly of failures in sound identification, synthesis, and association of meaning and symbol (Errors 6, 7 and 8). These difficulties were correlated with reversals and confusions of whole words (Errors 2 and 3) rather than of individual letters.

On the basis of these findings, a tentative definition of these forms of difficulty suggests itself. As has been emphasized, the difficulties occur less frequently in isolation than in association in affected children, though their relative severity varies.

First there is difficulty in dealing with shapes, recognizing them, reproducing them, and relating them to another, especially in the horizontal plane. This spatial or 'lateralizing' disability is manifest as relatively poor ability in performance tests, with the confusions mentioned on pages 162 and 164. In reading there is faulty word recognition or recall, especially of small words, and confusion of mirror image letters. The importance of errors of this type has been emphasized by Orton (1937) and Pearce (1953).

Secondly, either with or without spatial disabilities there may be difficulty in relating the sound or phonic unit to its written equivalent in synthesising sounds into words and in analysing words into sounds. This difficulty is found especially frequently in patients with expressive or receptive aphasia. It is manifest in reading and writing by confusion of vowel sounds, reversal of words and parts of words and inability to construct meaningful words even when the individual written components have been correctly sounded (Schilder, 1944).

Thirdly, there is difficulty in appreciating the meaning of either spoken or written words, and especial difficulty with relational words, for instance conjunctions, prepositions or auxiliary verbs, whose meaning in isolation is much more elusive than that of most verbs and nouns. These words were often omitted, reversed or confused with one another. The difficulty in perceiving words to be meaningful appeared to be closely related to the inability to deal with tests of classifying and of finding verbal equivalents for given words. It was most marked in patients with expressive and receptive aphasia and even when it was not associated with marked spatial difficulties, as in group (*c*), its presence appeared to preclude easy learning of reading or writing. In particular, facility in relating written word shapes directly to meaning failed to develop. The nature of this difficulty in perceiving the meaning of words is very difficult to define more precisely without becoming involved in philosophical speculation, but it is reminiscent of the defect of comprehension noted by Head (1926) in patients with 'semantic aphasia'.

The observed difference in severity between the groups defined in terms of their scores on verbal and performance tests is in accordance with the findings of Schonell (1948). This author stresses that the spoken word is the symbol to which meaning is first attached and that written symbols acquire meaning only through their equivalence to the spoken. It would therefore be expected that difficulties with the basic symbols of communication (as in patients with expressive or receptive aphasia) would lead to reading problems of a more fundamental kind than would difficulties with visual symbols only. The inevitable association of reading and writing difficulties with acquired expressive and receptive aphasia was similarly explained by Head (1926).

The severity of the reading and writing difficulties in our patients appeared to be paralleled by their relative failure on tests of the ability to define and categorize, and that this latter operation seemed to be the most difficult verbal one for all three groups. This suggests that these failures may be closely related to the underlying conceptual difficulty in developmental aphasia. But clearly much work is required before it will be possible to define the nature of this conceptual disability more accurately and determine its relationship to the spatial difficulties on the one hand and the phonic and semantic difficulties on the other which are such prominent features of the condition. In the present state of knowledge it seems to us that there has already been more than enough speculation on the possibility that variations in the laterality of cerebral function may be responsible for developmental aphasia.

Summary

A description is presented of an investigation of 78 children of average intelligence, referred to a department of child psychiatry, who were found to have specific dyslexia and dysgraphia due to developmental aphasia.

The types of reading and writing errors encountered are described and classified. The frequency

with which retarded speech development, expressive and receptive aphasia and speech defects are found is emphasized. A high proportion of the patients, their siblings and their parents were found to be ambidextrous. The behaviour disorders shown by the patients are described and the aetiological importance of educational difficulties in producing them is discussed.

The writing and reading difficulties tended to be more severe in patients with receptive or expressive aphasia. Three types of difficulty in reading and writing could be defined by relating the types of errors found to the failure of the patients on various sub-tests of the Wechsler verbal and performance scales. They were present in association in different degrees of severity in different patients. The difficulties appeared to be due to:

(1) Inability to perceive the relationship of shapes and letters in space and in reproducing them correctly; (2) failure to relate phonic and written symbols correctly to each other; (3) failure to perceive the meaning or significance of the written or spoken word. The severity of the learning difficulties appeared to be most closely related to the third factor, and it is suggested that this may be a pointer to the direction which further investigation of the underlying conceptual difficulties in developmental aphasia should take.

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RESORCIN POISONING

BY

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Resorcin poisoning in young children is rare but has been reported on a number of occasions, especially in the German literature. Nothen (1908) described poisoning in an 11-day-old child, suffering from pemphigus neonatorum, who was found dead in bed some hours after the application of 3% resorcin vaseline.

Kyrle (1915), in the course of treatment of a 2-year-old boy with eczema prescribed 10% resorcin lotion, and after two applications, at an interval of about 12 hours, the child's urine was noticed to be dark olive green on standing. His condition deteriorated rapidly, and when examined in hospital he was found to be cold, grey and cyanosed with a weak, irregular pulse. The pupils were dilated and there were mild, recurrent clonic fits involving the face and upper limbs. Within 12 hours the condition improved, the drowsiness and cyanosis diminished, but he developed a severe urticaria with raised temperature and severe dyspnoea requiring oxygen therapy. He made a gradual recovery. This case was interesting, because the resorcin lotion was applied to nearly intact skin.

Feigl (1918) described a 2-month-old child, suffering from generalized eczema, which had been treated with resorcin cream (concentration not mentioned). After three days the child became desperately ill, developed convulsions and died quickly.

Connerth (1925) had a patient 1½ years old with extensive eczema of the face and head, first treated with boric lotion and then with 5% resorcin zinc paste. After a few days the patient became drowsy, cyanosed and very ill, refusing all food. The haemoglobin fell to 45% and there was associated haemoglobinaemia and haemoglobinuria. The child died in convulsions.

Marie Haenelt (1925) treated a 3-week-old patient with napkin dermatitis using 5% resorcin vaseline. On the evening of the same day the baby was very restless, and next morning on admission to hospital was greenish-grey with severe cyanosis of the body generally. The urine was burgundy coloured, the blood was dark, with a haemoglobin of 53%, 2,900,000 R.B.C.s per c.mm. and bilirubin 2·8 mg. %. The child deteriorated rapidly and died within two days. The main post-mortem findings were haemorrhages in the pleura and pericardium, a sepia-coloured liver on section and an enlarged spleen. Death was due to methaemoglobinaemia.

In Becker's patient (1933) a child, aged 42 days, suffering from extensive intertriginous eczema, treated with resorcin paste 2% on one occasion only, there was vomiting with the development of an intense petechial skin eruption with the passage of dark coloured urine. There was general drowsiness, the haemoglobin fell in two days from 65% to 14% and the R.B.C.s from 4,000,000 to 1,000,000 per c.mm. The child died on the fifth day in spite of treatment with blood transfusion.

In the course of the treatment for an extensive intertriginous eczema in the genital area of a child aged 36 days, Liebenam (1935) prescribed resorcin paste. This was applied moderately thickly five to six times within 24 hours, and the next day the child became gravely ill, with a greenish-grey skin and intense general cyanosis. The child became unconscious with opisthotonos and a rapid respiration rate, the haemoglobin fell to 65%, and efforts to give blood intravenously were unsuccessful. The child died in convulsions two days after admission.

Wirth (1938) recorded a baby girl, 2½ months old, who, following treatment for diarrhoea, was admitted with restlessness and marked general cyanosis. The abdomen was tender and the liver and spleen were enlarged. The urine was yellowish-green. The haemoglobin was 84% and the blood serum had a dirty, dark chocolate appearance. There was a suspicion of poisoning, and the medicine which had been given for the diarrhoea was sent for analysis. The baby was treated with blood transfusion and given oxygen, but in spite of this the haemoglobin fell to 62% in the days following admission. The child then made a quick recovery, and was discharged on the twelfth day, apparently

quite well. Analysis of the medicine prescribed for the diarrhoea showed that it contained resorcin, which in error had been made up one hundred times too strong. The baby had had in all six teaspoonsful, equal to 150 centigrammes of resorcin.

Resorcin was proved by Bull and Fraser (1950) to have a definite anti-thyroid effect when administered parenterally. They described three cases in adults where myxoedema had followed prolonged application of resorcin ointment to varicose ulcers. The radioactive urinary iodine excretion tests in both cases showed an extremely low excretion, and an avid uptake by the thyroid gland. One of the patients had severe anaemia with a history of jaundice on two occasions, episodes suggesting haemolytic anaemia. Hart and Maclagan (1951) reported similar myxoedematous symptoms in an adult case with extensive varicose ulcers.

Owing to the rarity of the condition and its possible tragic results, the following case appears worthy of record.

Case Report

A baby boy, D.W., aged 7 weeks, was admitted to Kingston Hospital on March 4, 1953. He was born on January 15, after a normal delivery, birth weight 6 lb. 11½ oz. (3,047 g.). The neonatal period was uneventful apart from slight conjunctivitis, which responded to penicillin locally applied. Breast feeding was easily established. Between February 6 and 20 the mother suffered from severe abdominal colic without diarrhoea or vomiting, and was treated medically by her family doctor. During this time the baby developed green and slimy motions, but continued to take the breast milk satisfactorily. There developed, however, a marked inflammation of the skin of the buttocks, scrotum and neighbouring parts, and when the baby attended the Infant Welfare Clinic on February 20 a bland ointment was prescribed. By February 27 there was no improvement, and by then the skin had broken down extensively over the napkin area. Calamine lotion was prescribed and applied for four days. On March 3 the motions had returned to normal, but the raw skin persisted. A new ointment was prescribed with instructions for it to be applied to the napkin area after bathing the inflamed parts with warm water. This ointment was applied on four occasions only, the last one between 9 a.m. and 10 a.m. on March 4. The mother noticed after the fourth application that the child shivered all over for about a minute, and in the belief that he had caught cold in the bath, dressed him quickly. This episode did not worry her unduly at the time as the baby generally had a poor circulation. Afterwards he took the 10 a.m. feed quite well and was placed in the pram. Throughout the morning he whimpered more than usual, but when seen at 11.30 a.m. approximately, was asleep and seemed to be all right. Between 1 and 2 p.m. the mother noticed a peculiar deep blue discoloration of the lips, eyelids and skin, with a yellowish colour intermingled. She called her neighbour, who nursed the baby for a time, ascribing the trouble to 'wind'. He improved a little, but refused part of the 2 p.m. feed, and when afterwards his condition deteriorated rapidly the mother brought him directly to hospital, where he was admitted at 3.30 p.m.

On examination the child was very ill with an intense, dusky-grey cyanosis and rapid, grunting respirations. There was no stridor and no intercostal recession (temperature 98·8° F., pulse 144 to 150 per minute, respiration 40 per minute).

The mouth and throat were clear, except for dusky cyanosis of the mucous membrane. The pulse was rapid, but no other abnormality was noted in the cardiovascular system. Respirations were rapid, but there was no evidence of pneumonia. The abdomen and central nervous system appeared normal.

There was an extensive dermatitis covering the whole napkin area, the rash having a purplish colour in line with the rest of the skin of the body and mucous membranes. There was marked oedema of the shaft of the penis. There was a scattered maculo-papular eruption of the lower buttocks, arms and forearms.

The urine was scanty, but a small amount obtained for examination was of port-wine colour and contained blood on routine ward testing.

A diagnosis of haemolytic anaemia with haemoglobinuria was made, and blood findings were: Hb (?) 80% (serum turbid and coloured), R.B.C. 4,000,000 per c.mm., W.B.C. 36,000 per c.mm. A blood transfusion was set up using group O, Rh-negative blood, but after 50 ml. had been given it was discontinued.

During the next day the child remained dangerously ill (temperature 100° F., pulse 160 per minute, respirations 40 per minute).

The Hb at 11.30 a.m. was 64% approximately (serum highly coloured and turbid), W.B.C. 40,000 per c.mm. (polymorphs 47%, lymphocytes 47%, monocytes 5%, eosinophils 1%). Blood transfusion was restarted, and 250 ml. of group O Rh-negative blood given. At 3 p.m. (with blood transfusion in progress) Hb was (?) 40%, R.B.C. 2,100,000, W.B.C. 36,000, platelets 300,000 per c.mm. The fragility of red cells was within normal limits.

The dermatitis was treated with calamine lotion and penicillin was administered parenterally.

On March 6 the child remained very ill, but if anything there was a slight improvement (temperature 101·6° F., pulse 150 per minute, respirations 40 per minute). The cyanosis of the mucous membranes and limbs was less intense. The papular eruption had spread to the abdomen, and there was a fresh outcrop of lesions on the arms and forearms. The spleen became easily palpable. The urine was thick, dark brown, with a greenish deposit. The blood serum was reddish-brown.

At 8 p.m., as the child did not have evidence of a severe infection and as the cause of the haemolytic anaemia was not apparent, I had a personal interview with the mother, when she was asked to bring up all the medicines and ointments which she and the child had had. She exactly repeated the history as originally told, and reaffirmed that she herself had only had medicine from

her doctor for colic. One of the ointments which she produced had been dispensed by a local pharmacist on a prescription from the Infant Welfare Clinic and could not immediately be identified. This was the last ointment prescribed by the Clinic and applied on four occasions.

In the morning the hospital chief pharmacist, in consultation with the retail pharmacist by whom the ointment had been dispensed, discovered that he ointment was in fact unguentum resorcin B.P. In all 2 to 3 drachms had been removed, and this had presumably been applied to the affected area of skin. As unguentum resorcin B.P. contains 12·5% resorcin in a base consisting of glycerine, wool fat and soft paraffin, the amount of resorcin used was between 15 and 20 grains. This evidence pointed to resorcin as the source of the haemolytic anaemia.

The biochemical report now stated that the blood serum was reddish-brown and on spectroscopy there was a band at 630 millimicrons typical of methaemoglobin. The urine was dark brown and slightly cloudy. Centrifugation caused the separation of a dark green amorphous deposit, with a dark brown, clear supernatant fluid, which on spectroscopy showed two bands of oxyhaemoglobin. Porphyrins were not present, nor reducing substance. Protein tests were strongly positive. Tests suggested that the brown colour was due partly to melanin and the green to oxidation products from phenols. The most likely cause was suggested to be poisoning from a coal-tar derivative.

The biochemical report confirmed the clinical findings, and a diagnosis of resorcin poisoning was confidently made.

On March 7 the Hb was 76%, temperature 99° F., pulse 134 per minute, respirations 44 per minute. As the cyanosis became less marked the jaundice became more noticeable. The spleen was still palpable, but much smaller. The child still took feeds badly and had frequent loose motions, so parenteral fluid therapy by intravenous drip was necessary to maintain fluid balance.

Good progress was maintained on March 8. Feeds were taken quite well. The diarrhoea had ceased. The haemoglobin, however, had fallen again to 46%.

On March 9 the papular rash which had been noted on the arms and trunk became more extensive, covering the entire trunk, face, scalp and limbs. The napkin dermatitis was slow in healing, the raw, inflamed area showing little, if any, response to local treatment.

By March 11 the good general progress was maintained. Haemoglobin was 40%, R.B.C. 2,400,000 per c.mm., and no methaemoglobin was detected on spectroscopy.

The urine was cloudy and faintly brownish with many greenish-brown casts. There was a trace of protein, and tests for phenols were positive. Urobilinogen was present but not in excess.

On March 12 a blood transfusion of 250 ml. of group O, rhesus-negative blood was given.

By March 13 the rash on the body had become extensive and confluent with superficial scaling of a psoriasiform appearance. Penicillin therapy was discontinued.

On March 16 breast feeding was again satisfactorily instituted. Apart from the extensive papulo-squamous skin eruption the child was making good progress. On March 17 this was sustained, and the Hb was 74%, and no phenol derivatives were detected in the urine. The good progress was maintained, and by March 26 the skin was extensively desquamated as large patches fell away. The scalp remained one thick mass of crusts.

On March 31 the baby was discharged from in-patient treatment. The skin of the trunk had almost completely desquamated apart from a few resistant scaly areas. The napkin area had healed. Oily calamine was applied to the face and trunk, and zinc and castor oil ointment to the buttocks.

On April 4 the child, attending as an out-patient, looked well and the mucous membranes appeared healthy. No thyroid swelling was noted. The scalp continued to be one mass of thickened crusts. As olive oil and calamine treatment of the scalp was producing no effects, it was decided to discontinue all treatment. A course of iron therapy was started by mouth.

On August 19 the child was well. There was still a small area of scalp crusting, which had not completely healed. Most of the crusted masses had, separated satisfactorily. The mother found, however, that if she applied water to any part of the body it produced a rash as though the child had been burned. She therefore made no attempt to wash him, merely oiled the skin.

A later report showed that the child was very well, and apart from the skin being rather sensitive, there was no other abnormality.

Comment

The Divisional Medical Officer on enquiry reported that at the particular infant welfare clinic where this patient had been treated, resorcin ointment had been prescribed in only a few cases and then in small amounts for refractory skin lesions. Apart from the patient described, no other had experienced any known ill effect.

This case, together with reports from the literature, illustrates the danger of using resorcin, even in the weakest lotion or ointment, on the tender skin of babies and young children. Absorption may be intense and lethal where the skin is broken, but the ointment may also be absorbed and produce serious effects in sensitive subjects, even when the skin is almost intact. Resorcin ointment should not be used in the treatment of napkin dermatitis, eczema or other skin eruptions in childhood.

Summary

The literature on resorcin poisoning in infants and young children is reviewed. A case of severe haemolytic anaemia with haemoglobinuria and a generalized papulo-squamous eruption due to resorcin poisoning is described.

I wish to acknowledge the valuable assistance of Dr. J. F. Lees, who with Sister J. Taylor and other members of the nursing staff of the children's ward, effectively carried out the detailed treatment. I record my thanks also to Dr. D. Stark Murray, Consultant Pathologist, and his staff for the various haematological and biochemical investigations, to Mr. A. G. Shaw, Chief Pharmacist, for his report on the offending ointment, and to Dr. J. W. Starkey, Divisional Medical Officer, North Central Division, Surrey County Council, for his cooperation.

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CORTISONE THERAPY IN ERYTHROGENESIS IMPERFECTA

BY

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A rare but distinctive condition, which may be called erythrogenesis imperfecta (Cathie, 1950) or infantile pure red-cell anaemia, is gaining recognition. The nomenclature is, however, confusing. For example, some cases have been reported in later childhood, rendering inappropriate the word 'infantile'. Again, the varied titles illustrate the confusion of terminology. In the widest sense, i.e., without special reference to the infantile type, this erythropoietic disorder has been denoted by erythrophthisis (Kaznelson, 1922), pure red-cell anaemia (Lescher and Hubble, 1932), congenital hypoplastic anaemia (Diamond and Blackfan, 1938), chronic congenital aregenerative anaemia (Smith, 1949), chronic idiopathic erythroblastopenia (Gasser, 1949), erythrogenesis imperfecta (Cathie, 1950) and anerythrocytogenic anaemia (Loeb, 1951).

Over 30 cases of infantile type (referred to here as erythrogenesis imperfecta) are on record (Josephs, 1936; Diamond and Blackfan, 1938; Kohlbry, 1941; Høyer, 1942; Rubell, 1942; Robson and Sweeney, 1948; Smith, 1949; Cathie, 1950; Lelong, Joseph Polonowski, Desmonts and Colin, 1951; Anderson, 1952; Donelly, 1953; Aldridge and Kidd, 1953; Kåss and Sundal, 1953; Verger and Léger, 1953; Fisher and Allen, 1953; Burgert, Kennedy and Pease, 1954; Bernard, 1954). These descriptions monotonously reiterate that hitherto the only treatment capable of prolonging life was regular, and usually frequent, blood transfusion.

The case which we refer to here has been fully described (Robson and Sweeney, 1948) from the clinical and haematological aspects. The ineffectiveness of iron and liver preparations was then emphasized, while the life-prolonging effect of frequent blood transfusions was graphically illustrated. More recently, Coles (1955) reported on the failure of cobaltous chloride to produce a haematological remission in this child. A dose of 50 mg. daily was used for a fortnight and followed immediately by 100 mg. daily for a similar period. During this treatment the haemoglobin level continued to fall and there was no increase in the reticulocyte count. Our recent preliminary results with oral cortisone in this patient have been unexpectedly gratifying and are described and discussed here.

Case Review

Before Cortisone Treatment. D.S., now aged 10 years, had since 18 months of age (September, 1946) received regular blood transfusions at approximately three-monthly intervals for eight years, up to the start of cortisone therapy. His two lowest recorded haemoglobin values (Sahli) were 20% (concurrent erythrocyte count, 1,230,000 per c.mm.) in September, 1946, and 14% in February, 1951. Reticulocyte counts varied between 0 and 0·3%, and leucocyte counts between 6,100 and 16,800 per c.mm. with normal differential counts. Platelet counts ranged from 200,000 to 250,000 per c.mm. Myelograms (Table 1) showed very few red cell precursors as the only consistent abnormality. Leucopoiesis and megakaryopoiesis were always normal. Hypocellularity of marrow, previously present, was not apparent in 1952, while a high percentage of lymphocytes, some of which were in retrospect erythrogones, was almost a constant feature. An early bone-marrow biopsy (September, 1947) was examined by Dr. R. G. Macfarlane, who considered that it exhibited an erythroblastic hypoplasia, almost amounting to aplasia. Unfortunately, a myelogram was omitted just before cortisone treatment.

Cortisone Therapy. By 1954 the patient had become so scarred from the incisions for blood transfusions that sites for successful transfusion required increasing deliberation. As there had been no response to cobalt therapy in 1951 (Coles, 1955), a brief trial of cortisone treatment, although empirical, seemed justified.

In early September, 1954, when about due for a transfusion, as his haemoglobin value had fallen to 34%, treatment with cortisone (50 mg., orally, daily) was begun (Fig. 1). During the next six months this dosage was maintained. His haemoglobin level rose steadily to 90% in three months and remained so for a similar period, unaided by blood transfusion or other treatment. Indeed, no further resort to transfusion has been necessary. As we were anxious to ascertain whether

* The late Dr. T. Robson.

TABLE 1

+ SERIAL MYELOGRAMS IN THE ERYTHRON ONLY

	Oct., 1946	Aug., 1947	June, 1949	April, 1951	Nov., 1952	April, 1955	June, 1955
Cortisone therapy (started Sept., 1954) ..	—	—	—	—	—	Stopped for 2 weeks	Full control
Proerythroblasts %	1	0·25	—	—	1	1·25	0·75
Normoblasts (%)	7	4·5	2·75	4·0	7·5	12·75	22·5
A. Basophilic	—	0·75	0·25	0·5	0·5	5·5	2·75
B. Polychromatic	—	2·25	0·75	2·75	2·0	5·25	6·5
C. Orthochromatic	—	1·5	1·75	0·75	4·0	2·0	13·25
Macronormoblasts	—	—	—	—	—	2·5	3·5
Myeloid-erythroid ratio	9·8	18·0	24·7	9·8	10·3	3·6	1·8
Erythroid mitosis (% of all nucleated cells)	—	0·1	0·25	—	0·25	0·5	1·5
Leuco-erythrogenic ratio	—	9·1	17·1	—	5·1	1·4	1·04
Lymphocytes %	30	9	20·5	48·75	20·5	5·25	5·5
Erythrogones (%)	*	6·0	*	*	7·0	5·0	4·5
Cellularity	Reduced	Reduced	Reduced	Reduced	Normal	Slight increase	Definite increase

*=included in the lymphocyte count.

The complete myelograms are omitted as the earlier ones have been reported (Robson and Sweeney, 1948), while in the later ones the most striking changes are in the erythron. The values for lymphocytes and the rather similar cells called erythrogones (haematogones) are included, since specific mention of the latter was not made in the previous communication.

there had been a cortisone-induced or spontaneous remission he was now admitted for more detailed haematological investigation while on and off cortisone therapy.

On March 7, 1955, he was admitted to hospital. For the next week the dose of cortisone was reduced to 25 mg. daily (Fig. 2) without any fall in the haemoglobin value. Treatment was now suspended and at the end of the next fortnight the haemoglobin level had dropped to 69%. Cortisone treatment was then resumed, using a dose of 75 mg. daily for the next two days. His haemoglobin value had now risen to 84%, where it was maintained for a further five days while receiving 50 mg. of cortisone daily.

Treatment was now stopped a second time and the haemoglobin value again fell. There was a steady decline to 62% by the end of a fortnight. Recommencement of cortisone therapy (50 mg. daily) was followed by a slow rise in the haemoglobin level to 70% by the end of three weeks. A week later it had reached 80% when he was discharged from hospital (May 17, 1955).

For the next three months at home he continued to take 50 mg. cortisone daily. At the end of the first month the haemoglobin level reached 88%. There was little further change till two months later (August 18) when it was 83%. The concurrent blood urea value, undetermined since early childhood, was unexpectedly found to be 60 mg. per 100 ml. This and subsequent results from blood were obtained by finger-prick as there were no accessible veins. Urine microscopy was normal and there was no albuminuria. The cause of this mild azotaemia, whether cortisone, transfusions, or the earlier anaemia of the disease, was obscure.

To decide if cortisone was responsible the dose was promptly reduced to 37·5 mg. daily. Six weeks later (October 3) the blood urea level, checked weekly, had dropped to 46 mg. per 100 ml. The dose of cortisone was now further reduced to 25 mg. daily. After almost two months on this dose (November 25) the blood urea value had fallen to 38 mg. per 100 ml. with no associated undue drop in the haemoglobin value (77%). At the time of writing (December, 1955) a further reduction in the dose of cortisone is under consideration.

Two other notable haematological features were observed during the administration of cortisone. These were an impressive reticulocytosis and a sustained hyperchromic macrocytosis. Both were studied in greater detail during the final restoration of treatment. The pattern of the reticulocyte response at this stage was difficult to explain as there were two very distinct spikes (Fig. 2). The first of these appeared on the twelfth day, following a steady rise from 0·6 to 7·9% and succeeded by a steady drop to 1·4% over the next week. The second peak (9·5%) occurred exactly one week later. After a further fortnight the reticulocyte count had steadily declined to 1%. Subsequent values have varied from 0·5 to 2%.

The development of hyperchromasia during treatment was striking (Table 2). The colour index before cortisone administration was invariably close to unity. Values of 1·3 and above first appeared about six months after the initial administration of cortisone but persisted in the two phases, each lasting a fortnight, off treatment, and also during later maintenance of treatment. Since macrocytosis, as judged by the blood-films, seemed to accompany this hyperchromasia, it was decided to determine the discrete blood values. The results during 'full' control with cortisone (July 11, 1955) were: haematocrit value, 37·5%; mean corpuscular volume, 120 cμ; mean corpuscular haemoglobin concentration,

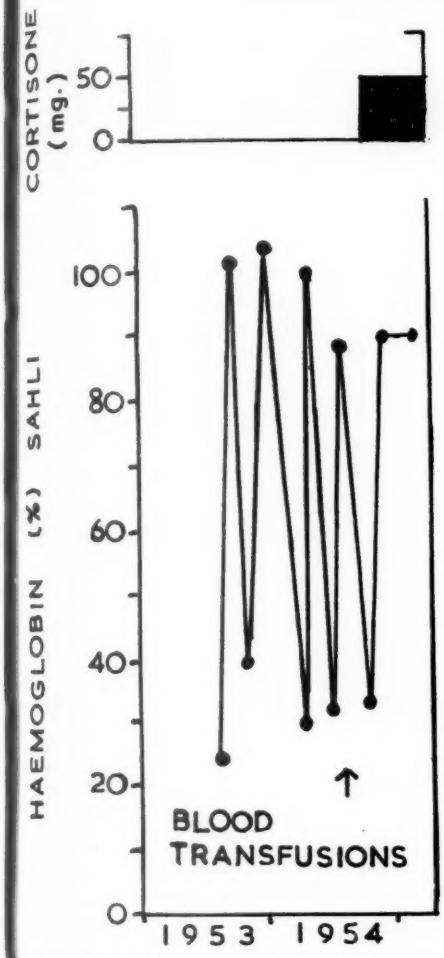

FIG. 1.—Cortisone treatment was begun at the point shown by the arrow.

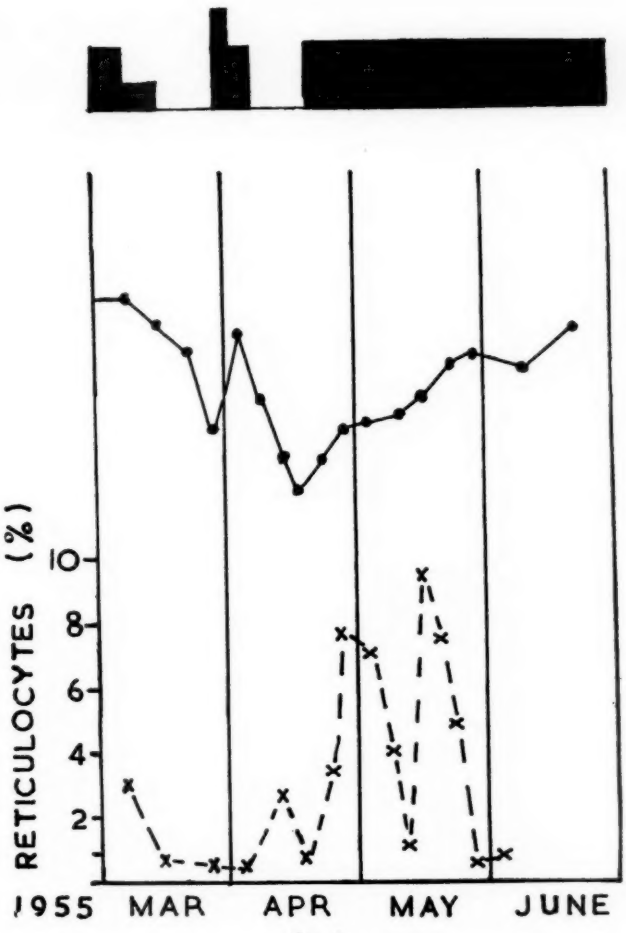

FIG. 2.

TABLE 2

RISE IN THE COLOUR INDEX DURING CORTISONE THERAPY*

Date	Hb. (%)	R.B.C. (m./c.mm.)	Colour Index
Before Cortisone Therapy			
Sept., 1946 ..	20	1·23	0·81
Aug., 1947 ..	29	1·44	1·04
Nov., 1948 ..	19	1·1	0·86
Sept., 1949 ..	20	1·23	0·81
Dec., 1950 ..	29	1·53	0·97
Nov., 1951 ..	42	2·08	1·01
Nov., 1952 ..	40	2·02	0·99
Feb., 1953 ..	46	2·22	1·04
During Cortisone Therapy			
Sept., 1954 ..	68	3·21	1·06
Oct., 1954 ..	76	3·52	1·08
Feb. 19, 1955 ..	87	3·91	1·12
March 15, 1955 ..	88	3·24	1·37
April 15, 1955 ..	75	2·82	1·34
May 6, 1955 ..	74	2·69	1·37
June 23, 1955 ..	83	3·10	1·36

* For simplicity, only a few results are recorded.

36% and mean cell diameter, 7·8μ, accompanied by a haemoglobin level of 85%, erythrocyte count of 3·11 millions per c.mm., colour index of 1·37 and a reticulocyte count of 1·5%. The corresponding blood-film showed moderate anisocytosis and slight poikilocytosis. These results are given in detail as they provide further evidence that the haematological improvement was not due to a spontaneous remission. If the latter had occurred then a normocytic, normochromic erythrocyte pattern should have accompanied the return of the haemoglobin level to the normal range.

From these observations, therefore, it was concluded that the administration of 50 mg. of cortisone daily, begun just when the usual blood transfusion was due, had by three months produced a haematological remission, which was maintained on this dosage for the next three months. Then, during two phases of cessation of treatment, each for two weeks, the haemoglobin value fell but rose again on resuming treatment. The second suspension of treatment was included: (1) To verify the repeatability of the observation. (2) To provide the

opportunity for a bone-marrow study when cortisone therapy had been stopped for a clear two weeks. The difference between this myelogram (April, 1955) and that obtained during 'full' haematological recovery (June, 1955) permitted a partial assessment of the bone-marrow changes produced by cortisone (Table 1). The salient change in erythropoiesis was a marked increase (2·0 to 13·25%) in the orthochromatic normoblasts but only slight in the macronormoblasts along with a moderate inverse trend for the more primitive erythroid cells (pro-erythroblasts and basophilic normoblasts), although the polychromatic normoblasts were scarcely altered numerically. Erythroid mitosis had increased from 0·5 to 1·5% while the myeloid-erythroid ratio was reduced from 3·6 to 1·8 and the leuco-erythrogenic ratio from 1·4 to 1·04. Although inspection of the earlier serial myelograms (Table 1) shows a trend towards normality of both erythropoiesis and cellularity of the marrow even before cortisone treatment was begun, there was no corresponding reduction in the volume and frequency of blood transfusions required.

During the administration of cortisone we have detected no adverse effects, apart from the mild azotaemia mentioned. Neither hypertension, cardiac enlargement radiographically, persistent glycosuria, nor the facies of Cushing's syndrome has appeared after more than one year on cortisone therapy. The results of detailed liver function tests were normal.

Discussion

We do not claim that cortisone has 'cured' or even corrected the basic disorder, partly because of our short-term study and partly since we have not produced a normocytic, normochromic, erythrocyte status. It can, however, be reasonably concluded that oral cortisone therapy has provided a convenient, superior and apparently safe alternative to blood transfusion. The disadvantages of the latter are the need for frequent short phases of treatment in hospital, the cosmetic scarring of the limbs from frequent cut-down procedures, the increasing technical difficulty, the unphysiological fluctuations in the haemoglobin level, the periodic invalidism just before the need for transfusion, and such hazards as transfusion reactions, cardio-respiratory stresses and acquired haemochromatosis. While the last-mentioned complication is considered to be inevitable, it is not clinically apparent in our patient, although the bone-marrow microscopy shows heavy deposits of stainable iron.

Until recently the only reliable treatment of erythrogenesis imperfecta was palliative repeated blood transfusion. This view remains unaltered despite the trial of numerous alternatives. Briefly, the list of ineffective treatments includes the conventional haemopoietic agents, various vitamins and hormones, and also short-wave diathermy to the long bones (Cathie, 1952). Splenectomy may have aided the remission in one patient, although the authors (Blackfan and Diamond, 1944) do not make this claim, while Cathie (1952) was unimpressed with the results of this operation. Spontaneous remission has been recorded (Blackfan and Diamond 1944; Burgert *et al.*, 1954). Although the oral administration of cobaltous chloride has been twice reported (Seaman and Koler, 1953; Fountain and Dales, 1955) as apparently effective in the adult type of pure red-cell anaemia, this treatment was ineffective (Coles, 1955) in our patient.

Recent attention has been focused on the use of cortisone and A.C.T.H. in erythrogenesis imperfecta. Nevertheless, the rather limited evidence available clearly indicates that this steroid therapy is far from uniformly effective. For instance, Cathie (1952) found it valueless in four cases; Smith (1953) likewise in two cases and Burgert and colleagues (1954) in one patient. Gasser (1951), however, reported the recovery, during cortisone therapy, of an infant with pure red cell anaemia, which followed measles. Two other favourable reports (Kåss and Sundal, 1953; Fisher and Allen, 1953) merit more detailed consideration.

Kåss and Sundal (1953) described definite haematological improvement from A.C.T.H. therapy in a girl aged 3 with erythrogenesis imperfecta, combined with defective myelopoiesis. They gave two brief courses of A.C.T.H. separated by an interval of 10 weeks. A complete assessment of the contributary effect of A.C.T.H. was, however, masked by a blood transfusion on the sixth day of the first course of 16 days, while the second course for 22 days was begun four days after a blood transfusion. During the second week of treatment, on each occasion, there was a distinct reticulocytosis with a maximal value of 8% in the second course, in contrast to values at all other times which were usually well below 2%. Bone-marrow examination just after the first course of A.C.T.H. showed an active normoblastic erythropoiesis with numerous macroblasts and a brisk myelopoiesis, while the myelogram just before the second course showed an ordinary number of marrow cells, scanty erythropoiesis and a striking abundance of lymphocytes, which were the usual features of all the earlier myelograms. Furthermore, after each course of A.C.T.H. the need for blood transfusion was prolonged by several weeks. Although not commented on by the authors, there was, as our study more clearly shows, an increase of the colour index above unity, due presumably to the steroid therapy.

Fisher and Allen (1954) reported their observations on a 3-year-old girl with erythrogenesis imperfecta, which was successfully controlled by

cortisone for at least eight months. Indeed the transient occurrence of polycythaemia left no doubt as to the potent erythropoietic action of cortisone. They begun cortisone therapy (50 mg. daily) about two weeks after a blood transfusion, and when the haemoglobin value had dropped to 87%. After two months of cortisone treatment this value rose to 113% and the administration of the drug was then stopped for one month. During treatment the maximal reticulocyte count (2·5%) was reached at the end of one month. A maintenance dose of 12·5 mg. of cortisone on alternate days sufficed to keep the haemoglobin level just above 80% throughout the next few months. Immediately after the first two months of cortisone therapy the marrow revealed a normal red cell series with maturation of normoblasts. There were 1·5% pro-erythroblasts and 30·5% normoblasts as compared with the myelogram before treatment showing erythroid hypoplasia (pro-erythroblasts, 7·0% and normoblasts, 2·0%).

Any extensive discussion on the possible modes of action of cortisone (and A.C.T.H.) in this condition would be too speculative to be valuable. Nor is there a ready explanation why only some cases, an as yet undetermined proportion, show haematological improvement from this drug. Their initial quantity and qualitative profile of erythroid precursors does not appear to vary significantly from that displayed by some cases which were refractory to cortisone medication.

Summary

A boy, aged 10 years, with erythrogenesis imperfecta, now successfully controlled for over one year by the oral administration of cortisone, is reported. This treatment was instituted just when his regular blood transfusion was indicated and no further resort to transfusion has been necessary. It was verified that the remission was due to cortisone and not spontaneous. After almost one year of cortisone treatment (50 mg. daily) mild azotaemia, but no other complication attributable to cortisone, was detected. Reduction of the dose to 25 mg. daily corrected the azotaemia without the recurrence of any severe degree of anaemia.

Under cortisone therapy an active and apparently normal erythropoiesis was obtained. The corresponding erythrocytic pattern in the peripheral blood, however, was odd, for a normal haemoglobin level was associated with erythrocytic hyperchromasia and macrocytosis. It was concluded that treatment with cortisone, although empirical and effective in some cases of erythrogenesis imperfecta only, provided for our patient a convenient, superior and apparently safe alternative to conventional and obligatory blood transfusions.

It is a pleasure to record our thanks to Dr. R. G. Macfarlane for his report on one of the earlier bone-marrow preparations; to Dr. T. A. J. Wickham for his review of the subsequent myelograms; to Dr. R. V. Facey and his staff for the numerous haematological investigations.

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AN UNUSUAL ILLNESS IN YOUNG CHILDREN ASSOCIATED WITH AN ENTERIC VIRUS

BY

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During August and September, 1954, 10 babies (seven girls and three boys with ages ranging from 3 to 14 months) were admitted to the Shadwell branch of the Queen Elizabeth Hospital for Children. They all showed a similar clinical picture, of uncertain aetiology, with irritability, fever, a maculopapular rash, enlargement of superficial lymph nodes, vomiting and diarrhoea. Changes in the cerebrospinal fluid (C.S.F.) were found. None was seriously ill at any time and all made a straightforward recovery.

Eight patients came from neighbouring East End (E.1 and E.14) districts of London. One patient came from South Ockendon, Essex, a housing estate to which many Shadwell families have moved, and one patient developed the illness while in hospital with a chest complaint.

Case Summaries

Case 1. R.C., aged 14 months, a girl, had had meningococcal septicaemia in March, 1954. She lived in E.1.

Four days before admission (August 11, 1954) she developed diarrhoea with watery brown stools; no blood or mucus. On the day of admission, she was very irritable, vomited all food and fluids, the bowels were opened four times, and she developed a rash.

On admission on August 15 her temperature was 102·4° F., pulse 136, and respiration 36. She was still very irritable, and had a fine, reddish-brown, discrete maculo-papular rash on the trunk, thighs and face, which faded on pressure, but no petechiae. The fauces were red, but without exudate. The cervical lymph nodes in the anterior and posterior triangles were enlarged.

No abnormality was detected in the cardiovascular and respiratory systems and in the abdomen. No meningism was found.

On August 15, the C.S.F. contained 12 cells (all lymphocytes), protein, 35 mg. per 100 ml., sugar, normal reduction, and a culture produced no growth.

On August 16 white blood cells numbered 12,800 (lymphocytes 68%), and on August 19, 8,200 (lymphocytes 80%).

No pathogens were isolated from the stools. A throat swab showed pneumococci and *N. catarrhalis*, and a nose swab pneumococci.

Glucose fluids were given for 24 hours.

The temperature ranged from 99 to 100° over the first five days and subsequently became normal. No vomiting after admission. Stools became well formed in three days. The rash gradually faded, first from the limbs, then from the face and trunk, and disappeared three days after admission. The child was discharged home, well, on August 23.

Case 2. M.R., aged 4 months, a girl, two days before admission screamed whenever touched. Her home was in E.1. She was very irritable, but took feeds and did not vomit. The stools were green. She developed a rash on the day of admission (August 22). On admission the temperature was 102·4° F., pulse 160, and respiration 36. She was very irritable, and had a fine, reddish-brown, discrete maculo-papular rash on the trunk, limbs and face; this faded on pressure. There were no petechiae.

The fauces and tonsils were red, without any exudate. The right tonsillar and left occipital lymph nodes were enlarged.

She had tachycardia.

Nothing abnormal was found in the respiratory system and abdomen, and no meningism.

The C.S.F. on August 22 contained 100 cells (polymorphs 26, lymphocytes 74), protein, 15 mg. per 100 ml., sugar, normal reduction, and no growth on culture. On August 30 there were four cells (polymorphs 2, lymphocytes 2). A white blood count on August 22 gave 24,000 (lymphocytes 64%) and on August 24, 13,400 (lymphocytes 70%).

A throat swab showed *Subtilis* and scanty pneumococci, and a nose swab diphtheroids.

The temperature became normal within 24 hours of admission and the rash faded in three days. The baby's general condition was good and she fed well throughout. She was discharged home, well, on August 31.

Case 3. L.H., aged 6 months, living in E.1, a girl, had cerebral palsy, chickenpox encephalitis when 4 months old, and otitis media. She was subject to

convulsions and was on phenobarbitone, grain ¼ t.d.s. She always lies with the head retracted.

She had been crying, irritable, restless and generally twitching for 24 hours. She had refused three feeds, but was not vomiting. The bowels were open three times with normal stools. The rash developed on the day of admission (August 23, 1954). On admission the temperature was 102·4° F., pulse 144, respiration 36. She was very irritable, with generalized myotonic spasms. She had a fine, reddish-brown, discrete, maculo-papular rash on the face, trunk, limbs and feet, fading on pressure, but no petechiae.

The fauces and tonsils were red without exudate.

The occipital and left cervical lymph nodes were enlarged. Nothing abnormal was noted in the cardiovascular and respiratory systems or in the abdomen.

She had generalized hypertonia, and head retraction unchanged from her previous stay in hospital with chickenpox encephalitis. Tension was normal in the anterior fontanelle.

The C.S.F. on August 23 contained 376 cells (polymorphs 78%, lymphocytes 22%), protein 15 mg. per 100 ml., sugar, normal reduction, and no growth on culture. On August 30, cells numbered 12 (polymorphs 4, lymphocytes 8).

A white blood count on August 23 gave 16,000 (polymorphs 48%, lymphocytes 37%, monocytes 15%).

A throat swab grew diphtheroids and *N. catarrhalis*, and a nose swab *Staph. aureus*. No pathogens were isolated from a rectal swab. The temperature became normal 24 hours after admission. The rash faded in three days and the convulsive movements subsided over five days. There was no vomiting or diarrhoea and the baby took feeds well and gained weight. Treatment with phenobarbitone was continued during the illness and after recovery.

Case 4. J.D., aged 7 months, a girl, living in Dagenham, Essex, was admitted on August 13, 1954, with a chest infection.

On admission her temperature was 99° F., and she was a pale baby. The fauces and tonsils were red. She had a paroxysmal cough, and rhonchi were heard at the bases of both lungs.

A chest radiograph showed nothing abnormal.

A white blood count gave 40,000 (polymorphs 16%, lymphocytes 84%).

A throat swab showed pneumococci and a nose swab *N. catarrhalis*.

The baby was treated with chloramphenicol as a case of pertussis for five days.

On August 24 her temperature was 102° F. (previously normal for one week), and she was very irritable, but had no diarrhoea or vomiting. On examination she had a faint, reddish-brown, discrete, maculo-papular rash on the trunk and arms, fading on pressure. She had no petechiae and no enlarged lymph nodes.

The C.S.F. on August 24 contained 84 cells (polymorphs 28, lymphocytes 56), protein 15 mg. per 100 ml., sugar, normal reduction, and no growth on culture.

A white blood count gave 20,000 (polymorphs 37%, lymphocytes 56%, monocytes 7%).

No pathogens were isolated from the stools.

The temperature became normal in 36 hours. There was no vomiting or diarrhoea. The rash faded in five days. The baby lost 3 oz. in weight while febrile, but gained 9 oz. subsequently before discharge. She was discharged home, well, on September 1.

Case 5. S.U., aged 9 months, a girl, living in E.1, was admitted on September 5, 1954. On admission she was feverish, very irritable and had been off her feeds for 24 hours before admission; she was not vomiting. The bowels were open normally (temperature 104° F., pulse 140, respiration 36). A fine macular rash, reddish-brown, on the trunk only, fading on pressure, had developed a few hours before admission, but with no petechiae. Nothing abnormal was seen in the throat. The cervical and occipital lymph nodes were enlarged.

The cardiovascular and respiratory systems were normal, as was the abdomen. There was no meningism.

The C.S.F. on September 4 contained 154 cells (mainly polymorphs), protein 30 mg. per 100 ml., sugar, normal reduction, and no growth on culture.

On September 17, the C.S.F. contained 18 cells (polymorphs 16, lymphocytes 2).

A white blood count on September 4 gave 37,000 (polymorphs 64%, lymphocytes 30%), and on September 7, 16,000 (polymorphs 29%, lymphocytes 62%). A blood culture showed no growth. A throat swab showed *Strep. viridans* and *N. catarrhalis*, and a nose swab *Staph. aureus*.

The temperature became normal in 24 hours. The child was very reluctant to take feeds for the first 48 hours, but had no vomiting or diarrhoea. The rash faded during the five days after admission, and she had recovered clinically by September 11. She was kept in hospital for social reasons until discharged home on September 22.

This case was treated with systemic penicillin and oral sulphonamides for the first three days in view of the possibility of a meningococcal infection.

Case 6. V.B., aged 12 months, a girl whose home was in E.14, was admitted on September 10, 1954.

She vomited four times on the day before admission and developed a rash on the trunk. On the day of admission, she vomited three times. The rash spread to limbs and face. She was feverish for 24 hours, and took clear fluids only. She had no diarrhoea. On admission her temperature was 99·4° F., pulse 136, and respiration 36. She was not an ill child, and was crying heartily.

A fine, reddish-brown, discrete, maculo-papular rash was seen on the trunk, limbs, face and soles of the feet, fading on pressure. She had petechiae on the face and chin. The fauces and tonsils were red, but without exudate. The cervical, occipital, axillary and inguinal lymph nodes were all enlarged.

Nothing abnormal was noted in the cardiovascular and respiratory systems or in the abdomen. She had no meningism.

The C.S.F. on September 10 contained 40 cells (lymphocytes 100%), protein 10 mg. per 100 ml., sugar, normal reduction, and no growth on culture. A second examination on September 20 showed 8 cells (polymorphs 4, lymphocytes 4).

A white blood count on September 10 gave a total of 20,400 (polymorphs 53%, lymphocytes 42%).

Platelets numbered 350,000 per c.mm. A throat swab showed pneumococci as also did a nose swab.

Her temperature varied from 98° to 99·8° F. for the first six days after admission. She did not vomit. The maculo-papular rash faded gradually during the 10 days after admission and the petechiae disappeared in four more days.

She was discharged home, well, on September 28.

Case 7. P.W., aged 4 months, a boy from E.1, three days before admission was very irritable and flushed. A rash appeared on the face and then spread to the trunk and limbs. He vomited twice two days before admission and once on the day before. He refused feeds for 24 hours. The bowels were normal. On admission on September 12 the temperature was 98·9° F., pulse 124, respiration 24. He had a discrete, reddish-brown, maculo-papular rash on the face, trunk and limbs, fading on pressure, but no petechiae. The fauces and tonsils were red, but without exudate. He had no enlarged lymph nodes. Nothing abnormal was found in the cardiovascular and respiratory systems or in the abdomen, nor any meningism.

The C.S.F. on September 12 contained 76 cells (polymorphs 19, lymphocytes 57), protein 25 mg. per 100 ml., sugar, normal reduction, and no growth on culture. A second specimen on September 22 showed 4 cells (polymorphs 2, lymphocytes 2). A white blood count gave 17,300 (lymphocytes 78%).

A throat swab grew scanty pneumococci and *N. catarrhalis* and a nose swab *N. catarrhalis*. No pathogens were isolated from a rectal swab. The baby continued afebrile after admission. He vomited twice and passed two loose stools in the first 48 hours. The rash faded in five days. There was no enlargement of the lymph nodes in this case at any time. He was discharged home, well, on September 25.

Case 8. M.J., aged 5 months, a boy from E.1, vomited three times and was flushed and irritable on the day before admission; on that day, stools were loose and a generalized rash appeared. He was admitted on September 14, 1954, when his temperature was 100° F., pulse 140, respiration 32. He was very irritable, and had a generalized, discrete, reddish-brown maculo-papular rash on the trunk, limbs, hands and feet, but few lesions on the face. The rash faded on pressure, and he had no petechiae. The tonsils and fauces were red, but without exudate. He had no enlarged lymph nodes. Nothing abnormal was found in the cardiovascular, respiratory or central nervous systems, nor in the abdomen.

A sample of C.S.F. taken on September 14 yielded cells nil, protein 10 mg. per 100 ml., sugar, normal reduction, and no growth on culture. Examination of the C.S.F. on September 15 gave 10 cells (polymorphs 2, lymphocytes 8) and on September 23, 2 cells (lymphocytes). A white blood count on September 14 gave 8,200 (polymorphs 30%, lymphocytes 66%).

A throat swab showed a scanty growth of haemolytic streptococci and pneumococci, a nose swab *Staph. aureus*, and a stool *Proteus vulgaris*.

The temperature became normal within 12 hours, and there was no further vomiting or diarrhoea. On September 21 small cervical lymph nodes on both sides were palpable. Petechiae appeared on the right cheek. The rash faded five days after admission.

The baby was discharged home, well, on September 25.

Case 9. T.B., aged 6 months, a boy, was admitted in September 20 from his home in E.14. For three days before admission he had been very irritable, feverish and difficult to feed, and two days before had spots on the stomach. One day before he had a rash on the face, limbs and trunk, but no vomiting and the bowels were normal. On admission his temperature was 100·2° F., pulse 132, respiration 30. He was very irritable, and had a fine, reddish-brown maculo-papular rash on the face, trunk, limbs and soles of the feet, fading on pressure.

The fauces were red, but without exudate. The cervical, occipital, axillary and inguinal lymph nodes were all enlarged. The cardiovascular, respiratory and central nervous systems appeared normal as did the abdomen.

A sample of C.S.F. on September 20 yielded 46 cells (polymorphs 4, lymphocytes 42), protein 20 mg. per 100 ml., sugar, normal reduction, and no growth on culture. On September 30 cells numbered 84 (polymorphs 10, lymphocytes 74), and on October 11 cells 14 (polymorphs 3, lymphocytes 11).

A white blood count on September 20 gave 17,000 (lymphocytes 70%).

Platelets numbered 310,000, and bleeding and clotting times were normal. The Paul Bunnell test was negative.

A throat swab grew *N. catarrhalis* and diphtheroids, and the nose swab *N. catarrhalis*. The temperature became normal 24 hours after admission. The baby remained very irritable for 48 hours. Petechiae appeared on both sides of the face and trunk and on the left arm one hour after the initial lumbar puncture and after both subsequent punctures, which were performed with the baby lying on the left side. The maculo-papular rash took 10 days to fade, and the petechiae four more days.

The baby passed two loose stools on October 3, but no pathogens were isolated from a rectal swab.

He was discharged home, well, on October 4. He was readmitted on October 11 for lumbar puncture and discharged after 24 hours.

Case 10. J.D., aged 4 months, a girl, was admitted on September 22, 1954, from South Ockendon, Essex.

Three days before admission she was very irritable, vomited after all feeds and passed eight green stools. Two days before admission a rash appeared on the face, and diarrhoea continued. On the following day she vomited four times, refused feeds, and was very irritable.

The rash spread to the body and limbs. On admission her temperature was 100·8° F., pulse 140, respiration 36. She was very irritable, and had a discrete, reddish-brown, maculo-papular rash, which faded on pressure, most marked on the face, but also on the trunk, limbs, hands and feet. The fauces and tonsils were red but without exudate. The occipital and cervical lymph nodes were enlarged. Nothing abnormal was found in the cardio-vascular, respiratory and central nervous systems, or in the abdomen.

A sample of C.S.F. on September 22 gave 220 cells (all lymphocytes), protein 15 mg. per 100 ml., sugar, normal reduction, and no growth on culture. On September 30 cells numbered 46 (polymorphs 4, lymphocytes 42), protein 40 mg. per 100 ml., and on October 8 cells were 10 (lymphocytes) and protein 15 mg. per 100 ml.

A white blood count gave 18,200 (polymorphs 25%, lymphocytes 75%).

Platelets numbered 232,000, and bleeding and clotting times were normal. A throat swab gave a scanty growth of haemolytic streptococci and pneumococci, a nose swab showed *Staph. aureus*, and no pathogens were isolated from a rectal swab. The Paul Bunnell test was negative.

The temperature became normal in 24 hours; no further vomiting occurred. Numerous petechiae appeared on the face, trunk and limbs after lumbar puncture in the first 24 hours. The rash faded 11 days after admission but the C.S.F. cell count did not reach normal limits until seven days later. The baby was discharged home, well, on October 12.

Clinical Features

All patients had a similar discrete, reddish-brown, maculo-papular rash on the face, trunk, extensor surfaces of the limbs and the soles of the feet, lasting for three to 14 days. Petechiae were seen in four cases and could be caused to appear by pressure. Nine patients were very irritable and nine were febrile. In eight patients one or more groups of superficial lymph nodes, chiefly occipital and cervical, were enlarged, and in eight the fauces and tonsils were red but no exudate was seen. Five patients vomited and four had diarrhoea, while five were especially difficult with their feeds. No enlargement of the spleen was noted. The child known to be subject to convulsions had numerous myoclonic spasms but the general condition was not otherwise altered.

The babies were ill for one to four days before admission to hospital, and the temperature fell one to five days after admission. Recovery was complete.

Laboratory Investigations

Lumbar puncture was performed on all cases shortly after admission. Cell counts ranged from 10 to 376 per c.mm. with 25 to 100% lymphocytes. Protein, sugar and chlorides were all within normal limits. Bacterial culture was negative. It was repeated on eight cases seven to 14 days later when the cells numbered 2-14 per c.mm.

The white cell counts in the blood ranged from 8,200 to 37,000 per c.mm. with 30 to 75% lymphocytes.

Platelet counts, bleeding and clotting times, when carried out, were normal. The Paul Bunnell test, on serum from two cases, was negative.

Throat and nose swabs from all cases failed to reveal any constant pathogenic bacteria, nor were any grown from stools or rectal swabs.

Virus Investigations

As the illness appeared limited in time, area, the age group involved, and was of uncertain aetiology, virus investigations were undertaken. Samples of faeces and serum, as shown in Table 1, were obtained from nine patients during and after their illness.

Faeces. A 20% suspension of each sample in buffered saline solution containing 100 units penicillin and 140 μg. streptomycin per ml. was centrifuged at 5,000 r.p.m. for a minimum period of one hour at 4° C. The supernatant fluid was checked for bacterial sterility before being used in virus investigations.

Tissue Culture. Fibroblasts grown from fragments of monkey testis implanted in chicken-plasma-lined tubes and epithelial cells grown from trypsinized suspensions of monkey kidney were used in virus isolation and neutralization tests. Synthetic medium 199 (Morgan, Morton and Parker, 1950) supplemented during the initial period of cell growth with 5% inactivated horse serum was employed. Tubes were incubated in stationary racks at 37° C. For isolation 0·1 ml. amounts of faecal suspension were inoculated into five fibroblast and five epithelial cell culture tubes and at least three passages were carried out before any suspension was considered to be negative. Fluids were harvested when cytopathogenic degeneration was evident or after seven and 12 days when absent or equivocal. Successful isolation in epithelial cell cultures with lessening of the toxic effects of the faecal suspensions was also accomplished when medium from a number of culture tubes was exchanged for a period of about two hours with faecal suspension which was then in turn replaced with fresh medium.

Five cytopathogenic agents (Table 1) were isolated from the faecal suspensions. The degenerative changes associated with these were noted in second passage tissue culture tubes four to five days after inoculation. In further passages the changes became more extensive and appeared in a shorter time. The changes initially were more readily apparent in fibroblast culture tubes and in these the five strains produced the same appearance with disruption and rounding of the cells in the immediate neighbourhood of the original tissue fragments. There was a gradual extension to the periphery but complete destruction only occurred in later passages. In epithelial cell cultures the extent of the degenerative change was more variable but with all strains it was limited initially to localized areas in which cells became small, rounded, opaque and finally disappeared, leaving irregular clear spaces surrounded by apparently normal cells. With further passages the destructive effect reached a stage at which it could not be distinguished from the effect produced by standard strains of poliomyelitis virus.

TABLE 1
SPECIMENS RECEIVED FOR INVESTIGATION AND THE VIRUSES ISOLATED

Case	No.	Sex	Age (mth.)	Duration of Illness (days) when Specimens Obtained		Virus Isolation from Faeces	
				Serum	Faeces	Tissue Culture	Suckling Mice
M.R.	2	F	4	6 20	3 6	+ +	– –
L.H.	3	F	8	–40* – 2*	–40* 4	– +	+† –
J. Dr	4	F	7	23 1 30	2	+	–
S.U.		F	9	5 95	–		
V.B.	6	F	12	22	2	–	–
P.W.	7	M	8	1 90	1	+	–
M.J.	8	M	5	8 19	–		
T.B.	9	M	6	2 21	2	+	–
J. Da	10	F	3	250	–		

* Previously in hospital with encephalitis following chickenpox.
† Identified serologically as a Coxsackie Group A virus.

No cytopathogenic agents were isolated from the serum obtained from patients during the acute stage of their illness.

Animal Inoculation. Litters of mice less than 1 day old were inoculated subcutaneously with 0·02 ml. amounts of each faecal suspension and at least two mouse passages carried out. Suspensions of whole mouse carcase were used for passage. In addition, tissue culture fluids of the various suspensions ranging from first to seventh passage were similarly inoculated. In these tests, as shown in Table 1, a strain of virus later identified serologically as belonging to the Coxsackie A group of viruses was isolated from a sample of faeces which had been obtained from Case 3 during a previous stay in hospital with encephalitis following chickenpox.

Mice, 4-6 weeks old, inoculated intracerebrally with 10^5 tissue culture doses of seventh passage fluid of the agent isolated from Case 4 showed no sign of illness.

Two rhesus monkeys were inoculated intracerebrally (0·6 ml.) and intraperitoneally (1 ml.) with pooled faecal suspensions. Monkey No. 1 received material from Cases 2 and 3 and monkey No. 2 material from Cases 4, 6, 7, 9. A further 1 ml. was given intramuscularly 11 days later and the monkeys were bled a month after the initial injections. Neither monkey had shown any sign of illness or temperature elevation. In tissue culture, cytopathogenic changes followed the inoculation of these two suspension pools but no effect was observed on the chorio-allantoic membranes of 10-day-old fertile hen eggs.

In the preparation of immune serum three guinea-pigs each received two intraperitoneal injections, at an interval of seven days, of third passage tissue culture fluid from Case 4. No reaction or temperature elevation occurred. After a further 11 days each was given intramuscularly 0·2 ml. of the same suspension emulsified in an equal volume of adjuvant (Arlacel A: Bayol F). An immune serum was similarly prepared against the agent from Case 9.

Serological Investigations. Neutralization tests were carried out in epithelial cell and to a limited extent in fibroblast cultures. A single dilution of virus suspension (100 tissue culture doses—TCD_{50}) was tested against varying dilutions of serum or vice versa. Equal volumes of the serum and virus dilutions were mixed and left at room temperature (about 22° C.) for one hour. After this time 0·1 ml. volumes were inoculated into two or four tubes per dilution. Tubes were examined from the third to the sixth day after inoculation.

Tests with the five newly isolated agents and the post-inoculation monkey and guinea-pig sera showed that the agents were closely related immunologically (Tables 2 and 3), but attempts (Table 4) to identify them using (1) specific antiserum against the three types of poliomyelitis virus, individually and combined into one pool, (2) pools of specific antiserum against the A and B groups of Coxsackie virus, (3) herpes simplex antiserum and (4) antiserum against three immunologically distinct strains of enteric cytopathogenic human orphan (ECHO) viruses were all negative. The post-inoculation monkey serum contained no antibody against any type of poliomyelitis virus. Tests with acute and convalescent phase serum from the children and a representative (C/4) strain were then carried out. These showed (Table 5) that a considerable rise in antibody level occurred during the course of illness in six patients, and that a high level of antibody was present in the convalescent samples of serum from two patients; in one patient no apparent response occurred. Tests with undiluted serum from the nine patients, either acute or convalescent depending

TABLE 2
TITRATION OF VIRUS SUSPENSIONS AGAINST 1 IN 10 DILUTION OF PRE- AND POST-INOCULATION IMMUNE SERA

Strain	No Serum	Monkey (C/2 + C/3) Serum		Guinea-pig (C/4) Serum		Guinea-pig (C/9) Serum	
		Pre-inoculation	Post-inoculation	Pre-inoculation	Post-inoculation	Pre-inoculation	Post-inoculation
C/2*	—	2·5†	0	—	—	—	—
C/3	—	4·5	0·5	—	—	—	—
C/4	4	4	0·5	4	0	4	1·5
C/7	—	4·5	0	—	—	—	—
C/9	2·5	2·5	0	2·5	0	2·5	0·5

* = strain isolated from Case 2.
† = negative logarithm of the end-point in the titrations.

TABLE 3

TITRATION OF A SINGLE DILUTION OF VIRUS SUSPENSION AGAINST DOUBLING DILUTIONS OF IMMUNE SERUM

Strain	Tissue Culture Doses of Virus (TCD_{50})		Dilutions of Guinea-pig (C/4) Immune Serum		End-point
	Estimated	Final	1/200	1/400	
C/2	100	320	0/4*	4/4	1/280†
C/3	100	1,000	0/4	4/4	1/280
C/4	100	320	0/4	4/4	1/280
C/7	100	100	0/4	3/4	1/335
C/9	100	100	1/4	4/4	1/237

* Number of tubes showing cytopathogenic degeneration over the number inoculated.
† Estimated by Kaerber's method.

upon availability, against the three types of poliomyelitis virus showed that four already had antibody against Type 1 virus and one of these had antibody against Type 2 virus also.

Similar tests with the C/4 strain and (1) five samples of serum from healthy children less than 2 years old living near the hospital showed that four were negative and one positive with a titre of 1 in 64. (2) Ten samples of serum from healthy Southend children less than 3 years old were negative. (3) Five samples of convalescent serum from children less than 2 years old and living in separate areas, all with a clinical diagnosis of aseptic meningitis were negative, and (4) two batches of gamma globulin prepared at the Lister Institute of Preventive Medicine showed titres of 1 in 10 and 1 in 40 respectively.

Coxsackie Virus Investigations. Neutralization tests in newborn mice with the Group A strain of virus isolated from the first sample of faeces of Case 3 showed that all three sera from this patient had antibody against this virus but the convalescent samples of serum from Cases 2, 4, 6 and 8 had no antibody. There was insufficient serum from the other patients for these tests.

Complement Fixation Tests. Tests with a number of the convalescent samples of serum and antigens of the influenza A, B, C, the psittacosis-L.G.V. group, mumps, lymphocytic choriomeningitis and the RI-67 strain of APC viruses were negative, and leptospiral agglutination tests were also negative.

Filtration. A tissue culture fluid suspension of the C/4 strain of virus was readily filtered through a gradocol membrane of A.P.D. 94 mμ. No attempt has yet been made to measure more accurately the size of the virus particles.

Discussion

The nature of this sudden limited outbreak was puzzling in that it did not correspond with any familiar clinical condition. It was not recognized by general practitioners in the neighbourhood as a common occurrence, and the fact that the illness was confined to very young children with no evidence of older children in the same families being affected,

TABLE 4

NEUTRALIZATION TESTS WITH C/4 AND POLIOMYELITIS VIRUSES AGAINST A NUMBER OF IMMUNOLOGICALLY DISTINCT ANTISERA

Serum	Dilution	Viruses			
		C/4	Poliomyelitis		
			I	II	III
Monkey (C/2+C/3) ..	1/10	+	−	−	−
Polio Type I	1/10	−	+	−	−
Polio Type II	1/10	−	−	+	−
Polio Type III	1/10	−	−	−	+
Polio pool of 3 types ..	1/12	−	+	+	+
Coxsackie A pool (10 types)	1/80	−			
Coxsackie B pool (4 types)	1/10	−			
Herpes simplex	1/10	−			
Rende*	1/80	−			
Cornelis*	1/80	−			
Farouk*	1/80	−			

* New Haven echo viruses.

TABLE 5

NEUTRALIZATION TESTS WITH ACUTE AND CONVALESCENT PHASE SERUM OF PATIENTS AGAINST STRAIN C/4 AND THE POLIOMYELITIS VIRUSES

Case No.	Serum Day of Illness	C/4 Virus Neutralized by Dilution	Undiluted Serum against Poliomyelitis Viruses		
			I	II	III
2	6	64			
	20	512	+	−	−
3	−40	<4†			
	− 2	<4	+	+	−
	23	128			
4	1	32	−	−	−
	30	128			
5	5	8	−	−	−
	95	128			
6	22	512	−	−	−
7	1	8	+	−	−
	90	128			
8	8	<4	−	−	−
	19	<4			
9	2	32	+	−	−
	21	256			
10	250	256	−	−	−

* Previously in hospital with encephalitis following chickenpox.
† Reciprocals of the final serum dilutions.
\+ Indicates the presence of antibody.

was strongly against a diagnosis of rubella, measles or chickenpox. These diseases were not prevalent in the area at the time. In addition, the rash was too persistent and the patients too irritable for it to be rubella; there was no blotchiness or after staining and no coryza for it to be measles; and no vesicles for it to be chickenpox. Glandular fever was excluded on the grounds of limited age group, constant cerebrospinal fluid changes, the small, rather shotty lymph nodes and the character of the rash. Roseola infantum was excluded because the temperature did not fall as the rash appeared. The total white cell count and degree of lymphocytosis were too low for acute infectious lymphocytosis. Petechiae tended to develop readily in several of the children following lumbar puncture. As the bleeding and clotting times and the platelet counts were

within normal limits, the petechiae were considered to be traumatic in origin.

Virus studies were undertaken as (1) no pathogenic bacteria seemed to be implicated, (2) the minimal changes in the cerebrospinal fluid suggested a possible virus aetiology including non-paralytic poliomyelitis, and (3) the illness associated with a maculo-papular rash was reminiscent of the epidemic exanthem described by Neva and Enders (1954) and Neva, Feemster and Gorbach (1954). Attempts at isolation were confined to investigation of samples of faeces and serum obtained during the acute phase of illness. It is possible that agents were present in other bodily exudates also, but none was examined. The use of tissue culture in virus studies has become a convenient technique and from this outbreak five cytopathogenic agents were isolated from the six samples of faeces examined. These agents or viruses, as one strain was shown to be filterable through a gradocol membrane 94 mμ A.P.D., did not cause reactions following inoculation into monkeys, mice and guinea-pigs, or on the chorio-allantoic membranes of fertile eggs.

On first isolation these viruses appeared to propagate more readily in monkey testis tissue culture, but after a small number of passages gave rise to extensive cytopathogenic changes in monkey kidney tissue culture also. They were immunologically closely related to each other but distinct from a number of other viruses, including poliomyelitis and Coxsackie viruses. Having been isolated from faeces they come within the enteric group of viruses (Dalldorf, 1952; Ramos-Alvarez and Sabin, 1954). It is noteworthy that, though other tests were negative, increased antibody levels developed in six patients against the newly isolated strains of virus during the course of the illness, and high levels of antibody were found in convalescent samples of serum from two others. The remaining patient did not respond and it is possible that his illness did not come within the same category.

The evidence is suggestive that these viruses played a part in this outbreak. There is also some evidence that their appearance was not a localized incident, as low levels of antibody against them were found when two batches of gamma globulin made from pools of adult serum were examined. Further work on the aetiology of such outbreaks of illness is necessary, but there is no quick road to the solution of the problem in view of the known multiplicity of immunological types among these tissue culture cytopathogenic agents.

Summary

An outbreak of mild illness in 10 babies admitted to the Shadwell, E.1, branch of the Queen Elizabeth Hospital for Children is described. The principal features were irritability, fever, rash, enlarged superficial lymph nodes, reddening of the fauces and tonsils, vomiting, diarrhoea and changes in the cerebrospinal fluid.

Five strains of virus were isolated in tissue culture. These were found to be immunologically closely related to each other, but distinct from a number of other viruses.

Their role in the aetiology of this illness is discussed.

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CHROMATOGRAPHIC SEPARATION OF REDUCING SUGARS IN THE URINES OF NEWBORN BABIES

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The application of paper chromatography to the qualitative analysis of reducing sugars by Partridge (1946) has greatly simplified the detection of these substances in biological fluids. In particular it has provided an accurate and comparatively easy method of separating reducing sugars in the urine. This has proved of great value in the investigation of such a condition as congenital galactosaemia, about which disease there has been much recent interest (Bray, Isaac and Watkins, 1952; Hudson, Ireland, Ockenden and White-Jones, 1954; Cox and Pugh, 1954). It is now almost a routine procedure for the urine of a baby becoming ill with jaundice in the first few days of life and not thriving to be tested for reducing substances. Hudson and Ireland (1954) have, however, warned against reaching a hasty diagnosis of galactosaemia if galactose is found in the urine of such a baby.

There is little information in the literature about the physiological excretion of reducing sugars by newborn babies. Woolf (1951) said that small amounts of galactose and lactose are found in the urines of milk-fed infants, but he gave no figures. He also said that xylose is frequently present in normal urines, but rarely exceeds 3 mg./100 ml. Rubin (1954) stated that sugars may be found in small amounts in the urines of healthy infants in the early months of life, but he gave no details. Flynn, Harper and de Mayo (1953) found lactose in the urines of 9% of normal men and women.

This paper is a report of our findings of the examination by paper chromatography of the urines of 50 normal male babies.

Method

Specimens of urine were collected from an unselected group of 50 male babies born at full term at the Jessop Hospital for Women, Sheffield. All urines were collected within the first seven days of life.

The chromatographic technique employed was that described by Williams (1954), using triangular-shaped filter paper, a butanol-pyridine solvent and a benzidine reagent developer.

A standard solution containing known amounts of glucose, galactose, lactose and xylose was put up with each set of urines and an approximate quantitative estimation of the reducing sugars in the urines was made by comparing the depth of colour produced on the filter paper after it had been developed with that produced by the known concentrations of the sugars. If a urine specimen could not be chromatographed on the day on which it was collected, thymol was added and it was stored at − 20° C. Each urine was also tested with Benedict's qualitative reagent.

All 50 babies were breast fed. For the first two days of life they were put to the breast at approximately six-hour intervals, and after that feeding was 'by demand'. Occasionally glucose water was given in the first two days if a baby seemed thirsty. It was not possible to correlate the times of feeding with the times that the urines were collected.

Results

Eighty-one urines were collected from the 50 babies.

Twenty-two babies (from whom 34 urines were collected) showed no reducing sugar in any specimen. Four babies (five urines) showed an unidentified reducing substance only. Twenty-four babies (42 urines) showed one or more reducing sugar in 25 specimens.

Six urines contained less than 50 mg. lactose/100 ml., five contained 50-100 mg. lactose/100 ml. and four 100-250 mg. lactose/100 ml. Seven urines contained less than 50 mg. galactose/100 ml., and six 50-100 mg. galactose/100 ml. Three urines contained less than 50 mg. xylose/100 ml. and one 50-100 mg. xylose/100 ml. Seven urines contained two sugars each. Nine urines contained an unidentified reducing substance. Glucose was not identified in any of the urines examined. Four urines reduced Benedict's reagent to yellow or orange and three of these were specimens containing 100-250 mg./100 ml. of lactose, the other contained less than 50 mg./100 ml. of xylose and an unidentified reducing substance.

Table 1 shows the number of babies who excreted lactose, galactose and xylose or combinations of the sugars. Table 2 shows the ages of the babies when the urines were examined.

TABLE 1
NUMBER OF BABIES EXCRETING REDUCING SUGARS

Reducing Sugars	No. of Babies
Lactose	14
Galactose	13
Lactose and galactose	6
Xylose	4
Xylose and lactose	1

TABLE 2
AGES OF 50 BABIES WHEN URINES WERE EXAMINED

	Day of Age in Babies Examined						
	1st	2nd	3rd	4th	5th	6th	7th
No. of urines containing lactose	1		5	1	7	1	
No. of urines containing galactose			4	1	6	1	1
No. of urines containing xylose			3		1		
Total no. of urines containing reducing sugars	1	0	9*	2	10*	2	1
No. of urines containing no reducing sugar	14	6	10	3	9	5	9
Total no. of urines examined	15	6	19	5	19	7	10

* Three third-day and three fifth-day urines contained both lactose and galactose. One fifth-day urine contained both lactose and xylose.

Discussion

As shown above, 24 out of 50 normal male babies excreted a reducing sugar at some time during the first seven days of life, and four babies excreted relatively large amounts of lactose (100-250 mg./100 ml.); the urines of three of these babies reduced Benedict's reagent to yellow or orange. Our numbers are too small for any firm conclusion to be reached, but Table 2 shows that the sugars were excreted mainly on the third to the fifth days of life, and less sugars were found on the first, second, sixth and seventh days.

The source of the lactose and galactose in the urines of the babies was presumably the gut. Flynn *et al.* (1953) thought that this was the most likely source of the lactose which they found in the urines of normal men and women, although in pregnancy and the puerperium, when considerable lactosuria was found, they thought that the probable cause was the reabsorption of lactose from the secreting mammary glands into the blood. If the lactose and galactose which we found in the urines of our babies was of alimentary origin it is not surprising that only one out of 21 urines collected on the first and second day of life contained a sugar, because the babies' intake of milk on the first two days of life would be very small. The one baby that excreted lactose on the first day of life was put to the breast twice a day, but we do not know the time of collection of the specimen in relation to the feeds. By the third, fourth and fifth days of life the babies would be taking more from the breast and this is when the maximum number of sugars was found. Lactose is normally hydrolysed to glucose and galactose before absorption, and if it is absorbed unchanged it cannot be metabolized and is excreted by the kidney. Why hydrolysis should not occur we do not know; there is no evidence of a deficiency of lactase in mature infants (Smith, 1951).

Galactose after absorption from the gut is usually metabolized to glycogen in the liver, but Hartmann, Grunwaldt and James (1953) have shown that in infants after milk feeds as much as 40% of the blood sugar may be galactose. If the renal threshold for galactose was exceeded galactosuria would result. Tolerance to ingested galactose is used as a test of liver function (Roe and Schwartzman, 1933), and as it is known that the liver of the newborn is functionally inefficient (Yudkin, Gellis and Lappen, 1949) this factor may have played a part as a cause of the galactosuria. That this may be so is suggested by the finding of maximum excretion of sugars on the third to the fifth days of life when physiological jaundice, now thought to be the result of liver inefficiency (Mollison, 1948), is at its height. By the sixth and seventh days physiological jaundice has usually faded, indicating liver 'recovery' and it is of interest that we found fewer sugars on these days.

Xylose is not a constituent of milk and it is likely that in the four babies in whom this sugar was found it had an endogenous origin.

Summary

The urines of 50 normal male babies were examined for reducing sugars by paper chromatography.

Twenty-four babies excreted either lactose, galactose or xylose or a combination of these sugars at some time during the first seven days of life.

The possible cause of these findings is discussed.

We have much pleasure in thanking Professor R. A. McCance, F.R.S., and Dr. J. L. Emery for help and advice in the preparation of this paper. We also thank Miss E. Finch for biochemical facilities. The babies were under the care of Dr. T. Colver and Professor R. S. Illingworth to both of whom we are also grateful for their helpful criticism.

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OBSTRUCTIVE HYDROCEPHALUS IN CHILDHOOD

BY

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The differential diagnosis of obstructive hydrocephalus in childhood involves a consideration of two main groups of cases, cerebellar tumours and obstructive lesions of a non-neoplastic nature. The most common of the non-neoplastic conditions are stenosis of the aqueduct of Silvius and obliteration of the outlet of the fourth ventricle.

In the literature on obstructive hydrocephalus the radiological distinctions between the neoplastic and the non-neoplastic groups have been well drawn mainly by improved techniques in ventriculography. The pathological aspects have been described by Russell (1949), but their differentiation by clinical methods has not received as much attention. The distinction is important as the hydrocephalus in the non-neoplastic cases can usually be relieved.

Many cases of stenosis of the aqueduct and occlusion of the outlet of the fourth ventricle are initially diagnosed as cerebellar tumours. This review was carried out with the object of establishing a means of reaching the diagnosis by clinical methods with the aid of a plain radiograph of the skull.

Material

Twenty-three cases were studied, 15 with cerebellar tumours and eight with non-neoplastic obstructions; of the latter four were stenoses of the aqueduct and four occlusion of the foramina of the fourth ventricle. The ages in the two groups were comparable, varying from 3 to 15 years.

The tumours were either medulloblastomas or astrocytomas, the obstructions in the fourth ventricle were all caused by arachnoid adhesions, the type produced by congenital atresia not being represented. The aetiology in the aqueduct stenosis group is not known but is usually a subependymal gliosis of uncertain origin.

Symptomatology

The length of the history is not always an accurate guide to the chronicity of the lesion. It might be supposed that in a chronic obstruction of the cerebrospinal fluid pathways the history would be longer than that of a rapidly growing tumour. However, five of the eight cases in the non-neoplastic group presented with symptoms of less than six months and the longest history was of two years' duration. The history in medulloblastoma was less than six months in all cases and in astrocytoma of the cerebellar hemispheres from three to 18 months.

The sudden onset and short duration of symptoms in aqueduct stenosis and fourth ventricular obstruction is often misleading. According to Lazorthes (1954) equilibrium can be maintained for many years. Decompensation may follow intercurrent illness, ventricular puncture or progression of the causal lesion quickly producing the familiar signs of intracranial hypertension.

In medulloblastoma the midline cerebellar syndrome of vomiting with or without headache and gross bilateral ataxia, mainly of the legs, was the typical history in most cases.

Astrocytomas being usually situated in one cerebellar hemisphere, there was often a history of staggering to one side and other evidence of unilateral cerebellar ataxia in addition to headache and vomiting.

Some features were peculiar to the history of the non-neoplastic group. Mental backwardness noticed by parents or teachers was quite marked in three of the eight cases. Putnam (1934) emphasized that a poor pre-operative mental state is associated with a higher operative mortality and a worse prognosis generally. Three children were brought to their doctors on account of increasing obesity, the symptoms of increased intracranial pressure, appearing some months later. This is due to hypothalamo-hypophyseal dysfunction, the pathogenesis of which will be referred to later. One other child had bouts of hypersomnolence. Russell (1949) has pointed out that these hypothalamic disturbances are an uncommon accompaniment of hydrocephalus so that the high incidence in this group is significant.

Writing of stenosis of the aqueduct, Pennybacker (1940) described a peculiar coarse tremor which is exaggerated during purposeful movements. This was seen in two of the present series and was the initial symptom in one. Deterioration of vision was a symptom in two cases, and incontinence of urine was an early symptom in one.

In one child a past history of meningitis pointed to the diagnosis of adhesions at the outlet foramina of the fourth ventricle.

Clinical Signs

An enlarged, globular head was sometimes a striking feature in the non-neoplastic group. However, in other cases the circumference was no greater than in the tumour cases. Robinson (1953) remarks that in older children the cerebral ventricles may be very greatly enlarged and yet the head circumference be increased by only one to two inches.

The general condition of the child is important; children with medulloblastoma usually look ill and have lost weight, whereas many of the more chronic non-neoplastic obstructions are found in plump children, sometimes pathologically obese. Papilloedema was seen in practically every case in each group; one case of aqueduct stenosis had secondary optic atrophy with visual failure. Nystagmus, present in most of the tumour cases, was not found in the non-neoplastic group. It was surprising how few cerebellar signs were produced by the greatly dilated fourth ventricle in cases with obliteration of the outlet foramina.

There was marked unsteadiness of gait in cases of medulloblastoma. The remaining cases in each group showed lesser degrees of impairment. Incoordination of the limbs was seldom seen in the non-neoplastic cases and never lateralized; it was the rule in tumour cases and often lateralized.

Radiology

The plain radiograph of the skull showed some striking differences between the two groups.

In the infant the effects of raised intracranial pressure are increased convolutional markings and widening of the sutures with enlargement of the skull. Sutural expansion occurs readily in the infant so that papilloedema is not a feature of hydrocephalus at this age. In childhood expansion occurs less readily and after nine years further evidence of raised intracranial pressure may be seen consisting of decalcification and erosion of the posterior clinoid processes. In the younger child these structures are protected from pressure by sutural expansion.

When the raised intracranial pressure is due to obstructive hydrocephalus the pituitary fossa may expand (Fig. 1). As pointed out by Bull (1953), this enlargement is rare under 10 years of age. Twining (1939a) has shown that the pituitary fossa enlargement is due to the pressure of a dilated third ventricle (Fig. 2) and is found in the more chronic cases of obstructive hydrocephalus. The dilated third ventricle and expanded pituitary fossa were features in those cases of chronic hydrocephalus presenting with evidence of hypothalamo-hypophyseal dysfunction.

FIG. 1.—Straight radiograph of the skull in a child aged 11 years with aqueduct stenosis showing increased convolutional markings, widened suture lines and enlargement of the pituitary fossa.

Davidoff and Epstein (1950) conclude that astrocytoma of the cerebellum produces more marked radiological change than medulloblastoma, but quote only one tumour case with any sellar change. In arachnoiditis of the posterior fossa, five of their 10 cases had enlargement of the sella

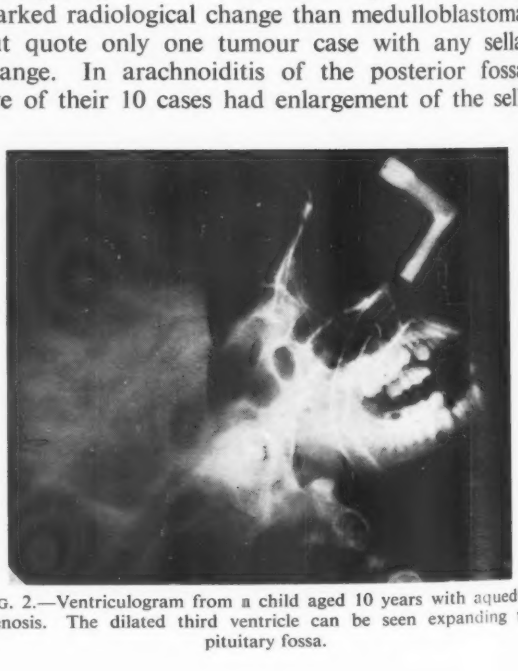

FIG. 2.—Ventriculogram from a child aged 10 years with aqueduct stenosis. The dilated third ventricle can be seen expanding the pituitary fossa.

while in aqueduct stenosis only two out of 13 had a normal sella.

In the present series all cases in the non-neoplastic group over 10 years showed erosion of the posterior clinoids and expansion of the pituitary fossa, whereas neither change was seen in any of the tumour cases. Presumably this is due to the rapid progress of medulloblastoma and to the fact that the astrocytoma, situated usually in one of the cerebellar hemispheres, obstructs the cerebrospinal fluid pathways at a relatively late stage in its evolution.

The main features of the conditions so far discussed are summarized in the Table.

TABLE

FEATURES OF NEOPLASTIC AND NON-NEOPLASTIC GROUPS

Medulloblastoma	Astrocytoma	Non-neoplastic Group
Short history	Longer history	Varying length of history
Ill appearance	Usually good condition	Head often enlarged, may be obese, often mentally retarded, may have visual failure and coarse tremor
Gross bilateral ataxia	Often unilateral cerebellar signs	Few cerebellar signs
Relatively slight changes in the plain radiographs	May have more chronic radiological changes	Radiological changes of chronic obstructive hydrocephalus

Some other less common conditions in the differential diagnosis may be considered. Midbrain gliomata are uncommonly associated with chronic hydrocephalus. They are characterized by lesions of cranial nerves, cerebellar, sensory and pyramidal pathways.

In so-called otitic hydrocephalus a history of preceding febrile illness or aural disease may be obtained. There is bilateral papilloedema with an absence of any other neurological signs except for an occasional sixth nerve lesion. The general condition in these children is usually very good.

Suprasellar cysts show calcification in the plain radiograph in about 75% of cases. Ventriculography is sometimes necessary for their diagnosis.

In the Arnold-Chiari malformation there is always evidence of congenital spinal deformity, either an overt meningocoele or meningomyelocoele or spina bifida occulta. Platybasia can be diagnosed from a plain radiograph of the skull. Ventriculography is essential in confirming the diagnosis before surgery.

In stenosis of the aqueduct the funnel or flask-shaped upper end of the aqueduct is characteristic (Fig. 3). Adhesions at the exit foramina produce an enlarged fourth ventricle (Fig. 4). In congenital atresia a grossly dilated fourth ventricle almost filling the posterior fossa has been described by

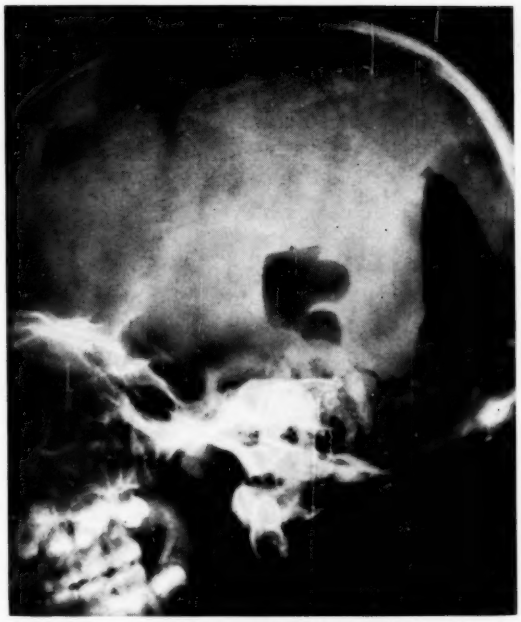

FIG. 3.—The flask-shaped upper end of the aqueduct projects downwards from the posterior end of the dilated third ventricle.

Taggart and Walker (1942), Benda (1954), Maloney (1954) and Gibson (1955). Occurring in foetal life it prevents the caudal migration of the transverse sinuses and torcular Herophili, the impressions of which become moulded on the parietal bones instead of in the usual position on the occipital

FIG. 4.—Hydrocephalus due to adhesions blocking the foramina of Majendie and Luschka in a child aged 5 years. The fourth ventricle is grossly dilated.

bone. The radiological appearance of this high lateral sinus was first described by Bucy (1939). These congenital cases may present for the first time in adult life.

The characteristic deformities in the ventriculogram produced by tumours of the cerebellum and brain-stem have been described by Twining (1939b) and Lysholm (1946).

Summary

The clinical differentiation of obstructive hydrocephalus in childhood is discussed. The cases fall into two main groups—neoplastic and non-neoplastic. In the former the most important conditions are medulloblastoma and astrocytoma of the cerebellum and in the latter stenosis of the aqueduct of Silvius and obliteration of the exit foramina of the fourth ventricle. A differential diagnosis can often be made on clinical grounds with the aid of a plain radiograph of the skull. This may enable the paediatrician to give a more definite prognosis at the first consultation.

We wish to thank the late Mr. C. A. Calvert, F.R.C.S., who had some of the cases in this review under his care, and Mr. D. Mehaffey, A.R.P.S., for the photographs.

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HYDRANENCEPHALY

BY

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From time to time various types of encephalodysplasia associated with cyst formation have been described. Under the term 'cystic aplasia', Turnbull (1904) described a case where both parietal lobes were involved. Hamby, Krauss and Beswick (1950) have reported seven infants with a related dysplasia under the term 'hydranencephaly'. In these infants the cerebral hemispheres were completely or almost completely lacking, the space normally occupied by them being replaced with cerebrospinal fluid. The meninges were in their normal situation. At birth the skull was normal in size in most of the infants but showed progressive enlargement after two to 12 weeks. The condition has also been described by Bettinger (1940).

The case reported here is a further example of bilateral cystic agenesis involving the prosencephalon and is described because of its extreme rarity.

Case Report

N.M., a Bantu male child aged 7 days, was admitted to this hospital with a history of having had diarrhoea and vomiting for three days. The child was born at home and no history was obtainable from the mother regarding siblings and other members of the family. The child had been breast fed for one day after birth but since then had taken only sips of water.

On examination the child appeared cold and cyanosed and was gasping for breath. It did not appear to make any spontaneous movements but it cried normally. There was an icteric tinge to the conjunctivae. The cardiovascular and respiratory systems appeared normal. The abdomen was soft and no masses were palpable. There was no neck rigidity and Kernig's sign was negative. Externally there were no signs of any congenital defect.

Whilst in hospital the child took fluid with great difficulty and died a few hours after admission.

Necropsy Report

The body was of a normal-looking Bantu male child and weighed 6 lb. 8½ oz. The conjunctivae and subcutaneous tissues were jaundiced. The skull circumferences were as follows (normal values for the newborn European child are given in parenthesis).

Occipito-frontal circumference	35·13 cm.	(35·19 cm.)
Sub-occipito-bregmatic ,,	31·9 cm.	(32·9 cm.)
Occipito-mental ,,	32·0 cm.	(32·53 cm.)

Skull and Vertebrae. Externally the cranial bones were normal in structure and the sutures were in the normal anatomical planes. The diploë were normal. The foramen magnum was intact and there were no defects in the vertebrae.

Brain and Meninges. On the skull being opened both cerebral hemispheres appeared to be completely lacking. The cranial bones were lined with meninges which appeared to be thicker than normal. There was a failure of development of the falx cerebri which was represented by a short fold of dura mater about ½ in. in length. The tentorium cerebelli was intact except, however, that the normal free anterior crescentic border was ill-defined and the dura appeared to blend with a thinner membrane covering the incisura tentorii. This membrane consisted of pia-arachnoid and was continuous with the pia-arachnoid layer lining the dura of the cranial vault. The dura of the tentorium was continuous anteriorly with that covering the lesser wing of the sphenoid in the usual way. The superior sagittal sinus and the transverse sinuses were intact. In view of the failure of development of the falx cerebri, however, there was no sign of the straight sinus.

The cavity above the level of the tentorium contained 19 oz. of amber coloured fluid and floating free in the fluid was a small, round, greyish-brown object, which consisted of a fibrous outer covering enclosing a red-brown pultaceous mass. There was a small dimple on the outer surface suggesting that it had been attached to the surrounding meninges but no definite evidence of such connexion could be found.

Below the tentorium there were a normal looking cerebellum, pons and medulla. All the cranial nerves were present on both sides, with the exception of the first. The upper level of the brain tissue appeared to be about the level of the third ventricle which was open superiorly. The opening of the aqueduct was visible. The structures forming the floor of the third ventricle were intact and can be seen in Fig. 1. These include the optic chiasma, infundibulum, tuber cinereum, corpora mamillaria and posterior perforated substance. The inferior surface of both lobes of the cerebellum was flattened. The falx cerebelli was intact.

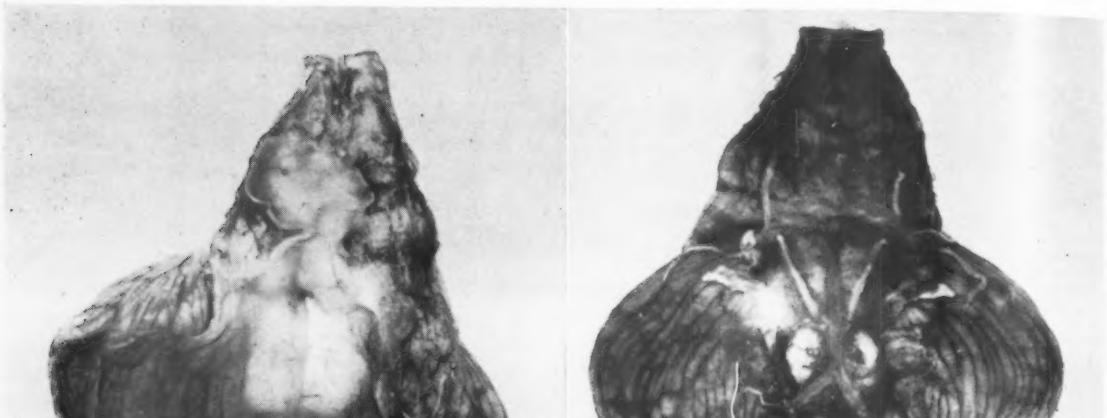

FIG. 1A. FIG. 1B.

FIGS. 1A. AND 1B.—The cerebellum and the structures forming the floor of the third ventricle.

Sagittal section through the cerebellum and mid-brain in the midline revealed a normal aqueduct and fourth ventricle. The spinal cord was normal at all levels.

The fluid from the cranial cavity had the following composition: protein, 2·92 g.%; chlorides, 660 mg. %; sugar, 34 mg. %; total bilirubin, 2·5 mg. %; polymorphonuclear leucocytes, 4 per c.mm.; lymphocytes, 10 per c.mm.

Apart from the infundibular stalk there was no evidence of any pituitary tissue derived from Rathke's pouch. The sella turcica appeared shallower than normal.

No abnormalities were detected in the remainder of the skeleton.

Heart. There was a large patent ductus arteriosus and a patent foramen ovale. Both, however, may have been incidental findings since the foramen ovale may remain patent up to 1 year of life and the ductus arteriosus up to 3 months.

Kidneys. The left kidney was of normal size. The right kidney was about one-quarter the size of the left and projecting from the surface were several small cystic swellings.

Adrenals. Both were small and hypoplastic, unlike the large adrenal which is present in the normal infant of 1 week.

Thyroid and Thymus. Both appeared normal.

Histology

Paraffin-embedded tissues were sectioned in the usual way and stained with routine haematoxylin and eosin.

The spherical object found loose in the cranial cavity consisted of blood clot with a fibrous tissue capsule. There were areas of calcification.

The meninges from the cranial vault were thickened and there was an incomplete layer of brain tissue on the inner surface. The right kidney showed many hyalinized glomeruli and numerous small cysts, but no cartilage, as is often found in malformed kidneys. The hepatic bile capillaries were distended, and there was much pigment in the Kupffer cells. Also the collecting tubules of the normal kidney were stained with bile.

The pancreas, thyroid and thymus appeared normal.

Discussion

When the skull was first opened in this case it was felt that this might be an example of anencephaly associated with normal development of the skull. Such cases are rare but an example is quoted by Wilson (1940). However, the presence of brain tissue attached to the meninges of the cranial vault, in a very thin incomplete layer, ruled this out since anencephaly is essentially an agenesis of the prosencephalon and is almost always complete. In the present case the optic nerves and the structures of the floor of the third ventricle were intact, all structures derived from the prosencephalon.

The aetiology of cystic aplasia of brain tissue is

unknown. Examples of hypoplasia usually involving one cerebral hemisphere have been attributed to toxi-infective lesions during intra-uterine life. Turnbull (1904) attributed his case of cystic aplasia to arrested development. In the present instance there was no evidence of any inflammatory process and the aetiology seemed to be an endogenous failure of development of part of the prosencephalon due to abnormality of the primitive germ plasm.

Potter (1952) in her monograph on the pathology of the foetus and newborn points out that in hydranencephaly the fluid is cerebrospinal fluid. However, in our case the composition of the fluid was quite different. The high chloride level suggests that there may have been an admixture of blood and C.S.F. The presence of the mass containing old blood clot suggests that there had been previous bleeding and this may have been responsible for the high protein content of the fluid.

Hypoplasia of the adrenals is an invariable accompanying feature in anencephaly, and was also found in this infant. It has been suggested that this hypoplasia is secondary to failure of pituitary development. Potter (1952), however, has pointed out that in the normal foetus the adrenals may be bigger than those found in anencephalics before the pituitary could produce any hormonal effects. The cause of the adrenal hypoplasia is still obscure.

The condition of hydranencephaly is not incompatible with life and cases have been reported in children more than three years old (Potter, 1952). The mental age remains at the newborn level. These infants, just as in some instances of anencephaly, may feed and cry normally. In addition spontaneous movements of arms and legs are common.

Diagnosis of the condition may be made during life by transillumination of the skull.

Summary

A case of hydranencephaly is described. There was almost complete absence of both cerebral hemispheres the space being occupied by fluid. There was only a thin, incomplete layer of brain tissue in the region of the vault. The parts of the brain derived from the rhombencephalon and the mesencephalon were intact.

I wish to thank Dr. R. E. Stevenson, Director of Provincial Medical and Health Services, Natal, for permission to publish this case note, and Dr. J. Wainwright, University of Natal, for the histological report.

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THE INCIDENCE OF INCOMPLETE DESCENT OF THE TESTICLE AT BIRTH

BY

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Descent of the testicle from the abdomen into the scrotum is known to occur at about the eighth month of foetal life. If the transition has not taken place at birth it may do so shortly after. It is said that movement can take place at any time up to puberty but very rarely afterwards.

Mothers, midwives and doctors are all aware that the scrotum of the newborn baby is usually well formed and contains both testicles. The proportion of infants in whom descent has failed or is retarded has apparently only once before been seriously studied. This paper records the results of examining over 1,700 infants in order to discover how often the testicle was undescended at birth. If the deformity was found the baby was seen again at intervals of a few weeks until descent was complete. The follow-up continues in a few instances where the testicle has not yet descended.

Previous Observations

Hofstatter (1912) examined 600 neonatal infants, 150 of whom were premature and 450 full-term. He found fully descended testicles in 68% of the former and 96% of the latter. He does not say, however, how he selected the infants for examination, nor does he mention at what precise age they were seen. In addition, his premature birth rate is obviously high in comparison with present British figures and, in fact, his definition of prematurity is a loose one, being based not upon the weight of the infant but upon its ability to thrive.

More recent writings do not always take note of Hofstatter's work and much confusion and contradiction appear. Counseller (1933) says, 'the testes are in their normal physiological position at birth in 90% of infants', whereas Deming (1952) asserts that it is estimated that '1% of the testes is undescended at birth'. Debenham and Baines (1954) give the incidence of incomplete descent in infants as about one in twenty. None of these statements has any meaning as it stands, for clearly, the incidence of the condition depends upon the maturity of the infant at the time of examination.

Conduct of the Investigation

The boys examined in this series were seen in the maternity department of a general hospital. A visit was paid to the ward on two set days in each week and every boy who had been born during the previous three or four days was examined. If an infant was stillborn or died within the stated period, the body was examined in the hospital mortuary. No differentiation was made as to whether the birth was by natural forces or by caesarean section; all were included. In this way a complete and consecutive series was obtained.

Exception, however, had to be made in two small groups of cases. If a mother with her baby was transferred to another hospital, or sent to her own home, within the first four days of birth, no attempt was made to trace them; such a random loss of cases, amounting to 28, would not appear to invalidate the accuracy of the results. Secondly, if a mother less than 28 weeks pregnant gave birth to a dead infant, examination was usually impracticable or impossible, for in such an instance, the foetus not being technically 'viable', it was not sent to the mortuary. On the other hand if the infant lived even for a short time it was transferred to the mortuary after death and seen there.

On rare occasions the mother and baby were sent to a nearby convalescent home. The babies were examined there but not until between the fourth and tenth days.

I examined each one of the infants myself, with the exception of 69 during the holiday month of August when the work was done by the gynaecological registrar. All stillbirths and neonatal deaths were seen by me, with the exception of four which were seen either by the paediatric registrar or by the

hospital pathologist. Owing to the relative ease of examination it is improbable that any case of incomplete descent of the testicle was overlooked (Fig. 1).

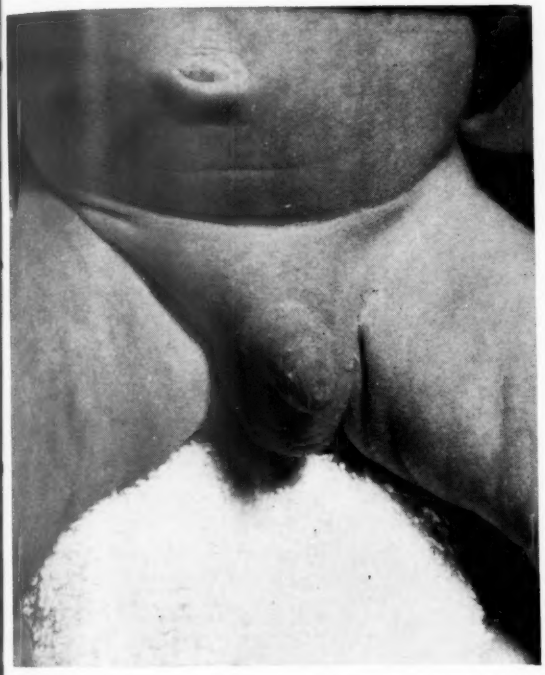

FIG. 1.—The appearance of the scrotum in a newborn infant weighing 5lb. 14oz. The right testicle presents as a swelling in the groin, the left is in the scrotum; the position of both was easily confirmed by palpation.

Method of Examination

It is a matter of common observation that the scrotum at birth is relatively larger than at any time in later life. In a full-term baby boy the length of the femur from pubic crest to knee joint is about 9 cm.; the scrotum when in a relaxed condition may be drawn down 6 cm. from the same point.

In addition, the infant at birth has comparatively little subcutaneous fat and the cremasteric reflex, so active in the young boy, is absent.

These three facts make examination of the testicle in the newborn an easy matter. No difficulty is found in deciding the position of the organ provided it is outside the external inguinal ring. With the thumb and forefinger the testis and epididymis, together of moderately firm consistency, can be held and gently drawn down a distance of between 4 cm. and 6 cm. from the pubic crest, sometimes even further. This distance can be measured with a ruler (Fig. 2 and Fig. 3).

Criterion of Incomplete Descent

The criterion of complete descent has been arbitrarily defined to be when the testicle can be drawn down to a distance of 4 cm. or more from

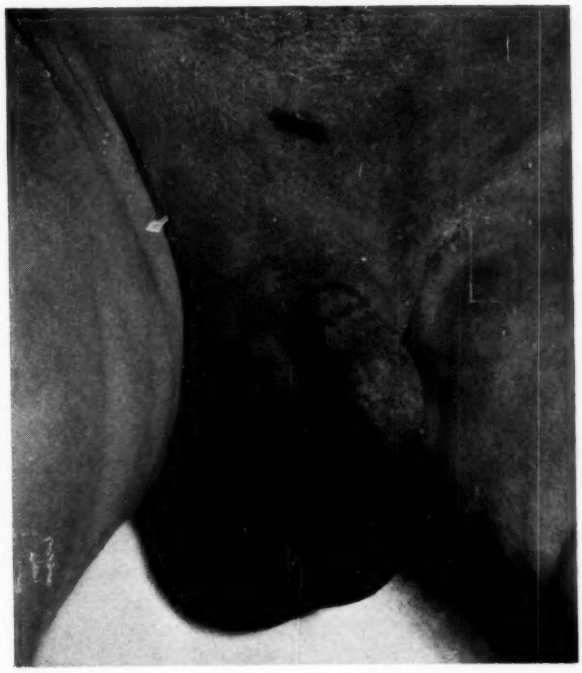

FIG. 2.—Scrotum of a full-term male infant, birth weight 7lb. 2oz. The black mark denotes the pubic crest.

the pubic crest. Any figure less than this was incomplete. The top of the pubic crest and the middle of the testicle were taken as the points of measurement. In premature babies, 5 lb. 8 oz. or less, the figure fixed was 2·5 cm. owing to the smaller size of these infants. In fact, in the full-term infant the testicle could almost always be drawn down considerably further than 4 cm. Even in the premature baby of just less than 5 lb. 8 oz. a distance of 3, 4 or even 5 cm. was usual, but, when the weight was under 4 lb., 2·5 cm. appeared to represent a fully descended testicle lying free in the scrotum. Some gradation in measurement is obviously necessary: the criteria mentioned above offer a reasonably reliable estimate of full and incomplete descent.

From another point of view the estimate appears to be valid. If the scrotum is contracted, the testicles may be forced upwards to lie in front of or above the external inguinal ring, but even so they can readily be manipulated and drawn down to reach 4 cm. below the pubic crest. If the same

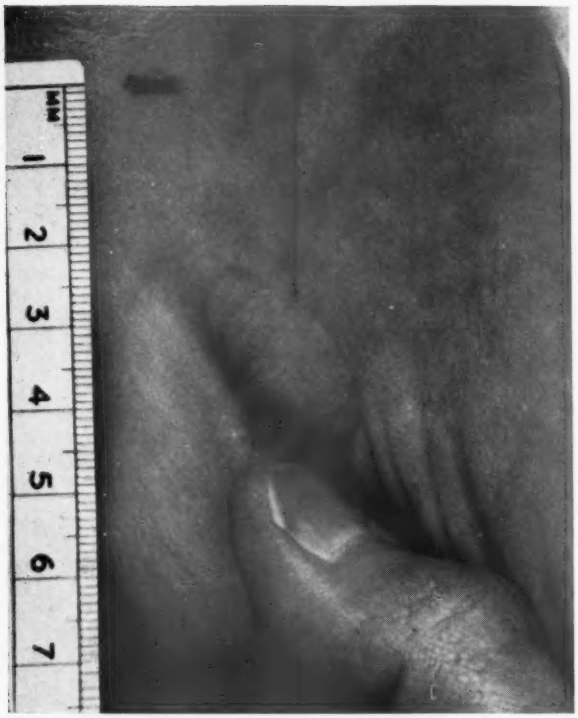

FIG. 3.—The same infant as in Fig. 2. The testicle can be drawn down to a position 6 cm. below the pubic crest.

infant is examined on another occasion when the scrotum is relaxed, the testicles will be found to be lying at the bottom of the scrotum and the distance from the pubic crest will then be about 5 cm.

The condition of the scrotum does, therefore, affect the measurements of the position of the testicles. But once a testicle has been drawn down 4 cm. subsequent examination always reveals that it will lie at, or almost at, the bottom of the relaxed scrotum. In addition, while the testicle is descending there is a certain rigidity of the cord and fixity of the organ; as soon as it has descended it lies free and mobile in the scrotum or can readily be drawn into it.

All cases of incomplete descent were checked on a second occasion and the follow-up was continued until descent was complete. A few cases, in which the testicle is not yet descended, remain under observation.

Results of Examinations at Birth

More than 1,700 infants were examined. The first 50 are not included in the tables given below because the criterion of what constituted normal descent had not then been established.

Conclusions are drawn from 1,500 consecutive full-term deliveries; the premature births (5 lb. 8 oz. body weight or less) which occurred during this series are classified separately, there being a total of 142.

Table 1 gives the results and shows the number of

TABLE 1

INCIDENCE OF INCOMPLETE DESCENT AT BIRTH

State of Infant	Weight (lb. and oz.)	Cases Seen	Incomplete Descent	Percentage
Premature ..	1 1–1 8	2	2	100·0
	1 9–2 0	4	4	100·0
	2 1–2 8	5	3	60·0
	2 9–3 0	8	6	75·0
	3 1–3 8	5	3	60·0
	3 9–4 0	11	6	54·5
	4 1–4 8	12	3	25·0
	4 9–5 0	41	7	17·1
	5 1–5 8	54	9	16·7
Total ..		142	43	30·3
Full term ..	5 9–6 0	130	16	12·3
	6 1–6 8	158	5	3·2
	6 9–7 0	256	8	3·1
	7 1–7 8	284	13	4·6
	7 9–8 0	270	6	2·2
	8 1–8 8	175	1	0·6
	8 9–9 0	135	0	—
	9 1–9 8	55	1	1·8
	9 9–10 0	20 (401)	1 (3)	5·0 (0·7)
	10 1–10 8	10	0	—
	10 9–11 0	3	0	—
	11 1–11 8	3	0	—
Total ..		1,499 + 1*	51	3·4
Grand total		1,642	94	5·7

* The figure +1 denotes a baby of full-term proportions who died shortly after birth from internal haemorrhage but was never weighed.

cases of incomplete testicular descent. The cases are divided according to body-weight at birth.

Any baby recorded as having incomplete descent was found to have either the left, or the right, or both testicles outside the scrotum (according to the measurements described above).

As would be expected, bilateral incomplete descent is found more commonly in premature than in full-term infants. The results are shown in Table 2. There were 94 cases in all and these were taken from the total number of newborn babies examined, 1,500 full-term and 142 premature.

Analysis of Results

The investigations undertaken and recorded in the accompanying tables show certain important facts which will be enumerated below.

Of all babies in this series, 5·7% were found to have one or both testicles undescended. In premature babies the incidence was 30·3%; in full-term deliveries 3·4%.

TABLE 2
SIDE AFFECTED IN 94 CASES

State of Infant	Weight (lb. and oz.)	Cases	Bi-lateral	Left	Right
Premature ..	1 1– 1 8	2	2	—	—
	1 9– 2 0	4	3	—	1
	2 1– 2 8	3	3	—	—
	2 9– 3 0	6	5	1	—
	3 1– 3 8	3	3	—	—
	3 9– 4 0	6	4	2	—
	4 1– 4 8	3	1	1	1
	4 9– 5 0	7	3	2	2
	5 1– 5 8	9	5	4	—
Total ..		43	29	10	4
Full term ..	5 9– 6 0	16	5	5	6
	6 1– 6 8	5	3	2	—
	6 9– 7 0	8	2	4	2
	7 1– 7 8	13	2	8	3
	7 9– 8 0	6	1	3	2
	8 1– 8 8	1	1	—	—
	8 9– 9 0	—	—	—	—
	9 1– 9 8	1	—	—	1
	9 9–10 0	1	—	1	—
	10 1–10 8	—	—	—	—
	10 9–11 0	—	—	—	—
	11 1–11 8	—	—	—	—
Total ..		51	14	23	14
Grand total		94	43	33	18

Descent was most common when the baby was between 3 and 6 lb. weight. It was rare when the weight was less than 2 lb., although one of the stillborn babies in this series, weighing 1 lb. 12 oz., had the left testicle fully descended (2·5 cm. below the pubic crest). Descent was almost always complete in babies more than 8 lb.

The incidence of incomplete descent fell steadily with the increasing weight of the baby at birth. In those over 8 lb. only 0·7% had the deformity.

In Table 1 no account has been taken of twin deliveries. There were in the series 19 twin boys and 20 cases of boy and girl twins, thus accounting for 58 boys in all. A comparative analysis is made below (Table 3) of the incidence of incomplete testicular descent in twin births and single births.

The numbers of infants involved in the twin series are too small to allow for any significant deductions to be made.

Bilateral incomplete descent was, of course, commoner in premature babies: the relative incidence is shown in Table 4.

The figures also suggest (Table 2) that descent took place a little later on the left side than on the right, 33 cases compared with 18. This inference was confirmed during routine examination of normal infants when the left testicle at birth was more often found to lie a little above the right than the reverse (in contrast to the adult position).

Follow-up

A follow-up of cases of undescended testicle could usefully be continued for many years—at least until after puberty. There is still doubt as to whether descent can take place up till adolescence, and if so, how often.

TABLE 3
TWIN AND SINGLE BIRTHS COMPARED

Maturity	Birth	Cases Seen	Incomplete Descent	Per-centage
Premature ..	Twin	30	7	23·3
	Single	112	36	32·2
Total ..		142	43	30·3
Full term ..	Twin	28	3	10·7
	Single	1,472	48	3·3
Total ..		1,500	51	3·4

TABLE 4
INCIDENCE OF BILATERAL INCOMPLETE DESCENT

Maturity	Cases	Bilateral	Percentage
Premature ..	43	29	67·4
Full term	51	14	27·5
Total	94	43	45·7

The result of watching newborn infants showed that the testicle often moved down during the first few days of life. Of the 94 cases undescended at birth, 23 were either stillborn or died in the neonatal period and almost all of these were premature. Of the remaining 71, the testicle descended in 38 (54%). Thirty-three are still being watched and in some of these the transition has taken place during subsequent months. Table 5 shows the maturity of the babies in whom the testicle descended within one month.

TABLE 5
DESCENT OF TESTICLE IN FIRST MONTH

State of Infant	Number	Died	Followed Up	Descent in One Month	Per-centage
Premature ..	43	20	23	14	60·9
Full term ..	51	3	48	24	50·0
Total ..	94	23	71	38	53·5

In the 38 infants in whom the testicle descended it reached the same low position as the opposite one and appeared to be of the same size and consistency. There was therefore a normal descent which was delayed beyond birth.

It is evident that the passage of the testicle from the abdomen into the bottom of the scrotum was normally rapid, taking only a few days or possibly two or three weeks. In full-term infants the testicle was very seldom in a half-way position (certainly less than 3·4%); it was either down or up. In the very few cases where it could only be drawn half-way down the descent was completed during the next

day or two. This rapidity of descent was also noticed in premature infants but movement often did not start until some days after birth.

Summary

Over 1,700 newborn male infants have been examined in a maternity unit in order to find out the incidence of incomplete descent of the testicle. In full-term deliveries it was 3·4% and in those born prematurely 30·3%.

An arbitrary definition of incomplete descent has been made. If this should become standard, the figures produced by different workers would then be comparable.

The babies have been classified according to weight. Descent was most common when the baby was between 3 lb. and 6 lb.

A follow-up of all cases of incomplete descent showed that in more than 50% the testicle reached the scrotum during the first month of life.

I wish to thank Dr. H. V. L. Finlay, physician in charge of our Paediatric Unit, for his enthusiastic encouragement and his stimulating criticism while this investigation was carried out.

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THE SIGNIFICANCE OF HYPOGLYCAEMIA IN THE NEWBORN INFANT OF THE DIABETIC WOMAN

BY

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The newborn infants of diabetic and of prediabetic women have morphological features which distinguish them from normal babies and which are of the greatest interest in the quest for further information about the aetiology of diabetes mellitus itself. In addition to these peculiarities of physical form, however, there are abnormalities of function during the first few days of life. Respiration may be established only with difficulty but it is more usual for the infant to start breathing normally. Progressive respiratory difficulty may appear shortly after birth and may assume a variety of forms such as unusually shallow breathing, choking due to the collection of mucus in the airway, or increasing embarrassment with laboured inspiration and costal indrawing. Other infants are subject to sudden attacks of respiratory arrest or slowing in which they become deeply cyanosed. These functional abnormalities are so diverse that they must differ in aetiology and they will be the subject of a later publication. In the literature, however, they are usually grouped together as 'cyanotic attacks' or 'colour changes' or 'respiratory incidents'. It is intended to use this terminology in the present paper, but in doing so the accuracy of the descriptive terms is not acknowledged. They have the virtue, however, of depicting a clinical picture to those who care for such infants.

The reduction of the foetal loss rate in pregnancy complicated by diabetes from a figure of over 40% less than a decade ago to around 15% in well controlled series today may be attributed to a combination of such factors as improved management of the diabetic state, stricter antenatal supervision, planned caesarean section with better anaesthesia and skilful supervision of the newly born child. Grave hazards are still met by the foetus both *in utero* and during the first few days after birth. There is also appreciable morbidity in the first week among the infants who ultimately survive.

The discovery that these infants commonly had remarkably low blood sugar levels led to the belief that the high morbidity and mortality might be due to hypoglycaemia. Alternatively a rapid and profound fall from a high intra-uterine level to a low normal neonatal level has been considered as being of aetiological significance. Although several investigations have been undertaken on this subject with particular reference to the neonatal mortality, some doubt still exists as to the clinical importance of hypoglycaemia and it was decided to attempt a final clarification.

Plan of the Investigation

Since 1948 90 infants born to proved diabetic women in the Simpson Memorial Maternity Pavilion, Edinburgh, have been studied personally. All have been observed continuously by experienced nurses and the nature of any abnormal incident has been recorded. Where these have lasted for longer than a minute or so they have been observed by an experienced paediatric house physician or by myself. All the abnormal incidents which persisted for 15 minutes or more have been observed personally and on repeated occasions the development and the course of the very brief incidents have been witnessed by myself.

In many of the earlier cases the blood sugar level was determined at regular intervals by a senior technician in the routine laboratory employing the method of Hagedorn-Jensen. Latterly the blood sugar level has been determined only if the course has been abnormal and only in the presence of symptoms. As only a proportion of the cases (about one third) was symptomatic and as a doctor was not always on the spot with the necessary apparatus when symptoms actually developed, the blood sugar level at the time of abnormal incidents is not available for each case. These blood sugar determinations form the preliminary part of the investigation and answer the first question, Do the incidents occur in association with hypoglycaemia? These findings must be considered also in relation to the second part of the study.

Although personal doubt was expressed about the need to give glucose to these infants after birth, its intramuscular use was found safe and it was given until 1952. Before 1948 glucose was given intravenously but, following a short and highly unsatisfactory experience of oral administration, a change was made in that year to the intramuscular injection of 20% to 50% solutions. The fact that some infants received glucose in no way invalidates the use of this group. Since 1952 its use has been confined to a few test cases.

Serial blood sugar levels of two groups of newborn infants were studied. The first consisted of 32 babies who conformed to certain criteria of normality (Farquhar, 1954) and the second was composed of 17 infants born to diabetic women. The two groups were dissimilar also in that the normal infants were delivered spontaneously by the vagina at full term, whereas the abnormal infants were delivered by caesarean section about the thirty-sixth week for reasons which will be published elsewhere by Matthew. The intention of the study, however, was to discover just how abnormal the chemical behaviour of the infants of diabetic women was, irrespective of the method of delivery, and to find out if the clinical behaviour of the latter group could be correlated with an abnormal pattern of movement in the blood sugar. For this purpose such differences may be ignored.

Blood sugar levels were determined in duplicate in the infants of each group at birth, half hourly until 2 hours and then two hourly until 6 hours. The levels were not followed beyond this point in the first day as a small pilot study had shown that levels stabilized by about that time. Thereafter the blood sugar was determined daily at 6 a.m. after a fast of eight hours. The chemical method and its accuracy were exactly as described previously (Farquhar, 1954). The determinations were done personally. With the exception of Cases 59, 69 and 70 (whose blood sugar pattern did not differ significantly from that of the group as a whole), none of these infants received glucose at birth and none of them was fed until day four or five. The exceptions received only 1 g. of glucose by deep intramuscular injection at birth.

All live born infants who died in the newborn period were examined post mortem and the findings recorded. The pancreas was subjected to special examination in each case by Dr. R. F. Ogilvie.

Results

'Respiratory incidents' were observed in 34 of the 90 infants studied and the blood sugar level at the time of symptoms was determined in 23 of these. The results in 21 of the symptomatic cases are recorded in Table 1 along with an indication of the severity and of the duration of the clinical disturbance. It is clear that no correlation exists between severity and hypoglycaemia. The blood sugar level may be high or 'normal' or low during continuous mild or severe disturbances or at the time of brief upsets. The opportunity arose in 1954 of comparing the widely different clinical progress of dizygous twins neither of whom had been given glucose. These observations and the blood sugar

TABLE 1
SYMPTOMATIC CASES AND COINCIDENT BLOOD SUGAR LEVELS

Case	Clinical Severity	Time of Incident	Chemical Method	Blood Sugar Levels (mg. %)
1	Delayed establishment of respiration	Birth	H–J	127
3	Continuous, moderate severe (inhalational)	Birth to 6 hr.	,,	66, 50, 70
6	Continuous, moderate severe (inhalational)	Birth to 6 hr.	,,	120, 298, 156
8	Continuous, mild	Birth to 10 hr.	,,	60, 78, 74, 74, 64
14	Continuous, severe (inhalational)	4 to 6 hr.	,,	138, 342
18	Continuous, moderate Fatal deterioration	Birth to 8 hr. 47 to 68 hr.	,, ,,	254, 180, 180, 86, 52, 114 Terminal level unknown
19	Continuous, severe initially with gradual improvement	Birth to 24 hr.	,,	(522), 160, 132, 66, 74, 74, 78, 84, 120, 128
35	Continuous to death	Birth to 2 hr.	,,	Terminal level 71
40	Continuous, moderate Sudden fatal deterioration	Birth to 3 hr. 50 min. 3 hr. 50 min. to 4 hr.	,,	43, 51, 57. Terminal level 62
41	Delayed establishment of respiration	Birth	,,	248
45	Continuous, mild	Birth to 2 hr.	,,	55, 52, 46, 63
46	Continuous, moderate	Birth to 9 hr.	,,	53, 58, 60, 62, 60
53	Continuous, moderate	3 to 6 hr.	,,	56, 60
69	Continuous, severe	Birth to Day 4	R	62, 60, 48, 79, 74, 60, 48, 43
84	Rapid fatal deterioration	16 hr.	R	265 (½ hr. after 1 g. glucose intramuscularly)
85a	Twin. Acute, severe, short	Day 3	R	111
98	Continuous to death	3 to 41 hr.	H–J	41. Terminal 68
100	Acute, mild, short	Day 6	H–J	123
101	Acute, mild, short	Day 3	H–J	94
102	Continuous, severe	Birth to 4 hr.	H–J	112, 74
103	Acute, severe, short	Day 4	H–J	43

The number of the case is that allocated to the pregnancy. As a number of these failed to result in the birth of a live child the case numbers exceed 100, although only 90 infants have been studied.

levels are recorded in Table 2 and again there is no relationship between clinical behaviour and the sugar value.

TABLE 2
K. TWINS

Time	Twin 1 (Case 90a)		Twin 2 (Case 90b)	
	Condition	Blood Sugar Level (mg. %)	Condition	Blood Sugar Level (mg. %)
2 hr.	Good	39	Very poor	75
7 hr.	Good	44	Slight improvement	58
14 hr.	Good	—	Poor	58
26 hr.	Good	73	Impending death	67

The result of the investigation into the serial blood sugar levels of normal babies has been published in detail (Farquhar, 1954). A wide range of values existed at any point after birth in the group as a whole and individuals showed variation from one time interval to another. These variations were greatest in the first six hours, and both the scatter of values in the group and the fluctuation of individuals within it became less marked as the infants grew older. This behaviour may be seen in Table 3 where the means of the duplicate readings have been taken to the nearest milligramme and provide sufficiently accurate data for the present study. No characteristic chemical behaviour existed and with the exception of Case 1 the blood sugar never fell below 40 mg. %.

The results in the group of infants born to diabetic women have not been published previously and are given in Tables 4 and 5. The scatter of values was again greater on the first than on other days and the range became less as the infants grew older. It is clear, however, that the pattern of movement was quite different from that in the normal group and that a characteristic fall in the blood sugar level occurred. The latter began at birth and it was maximum at one to two hours after delivery. In all these infants except Case 84 (who died at 16 hours) the blood sugar was rising again from four hours after birth and remained fairly stable thereafter.

TABLE 3
INDIVIDUAL PATTERNS OF MOVEMENT OF THE BLOOD SUGAR (mg. %) IN 32 NORMAL NEWBORN INFANTS

Case	Birth	Hours				
		½	1	2	4	6
A	86	62	66	62	57	66
B	—	72	—	43	50	65
C	82	71	54	56	68	—
D	56	59	57	62	70	66
E	71	71	72	69	70	69
F	71	82	60	49	51	47
G	55	44	50	51	50	45
H	59	69	80	70	58	67
I	—	—	40	38	32	39
J	77	95	105	68	56	71
K	87	84	69	69	59	61
L	69	79	102	85	72	67
M	53	53	53	55	62	72
N	71	68	61	64	61	60
O	68	69	60	56	58	42
P	95	74	63	61	64	63
Q	105	98	92	81	86	86
R	102	105	111	79	68	68
S	80	71	73	74	71	72
T	88	85	83	75	72	73
U	81	61	58	61	61	57
V	81	87	76	70	57	75
W	82	96	87	102	87	90
X	66	58	52	45	56	62
Y	78	83	77	81	79	68
Z	90	127	121	72	66	69
a	89	75	60	52	54	51
b	85	97	83	61	74	60
c	74	57	44	42	57	58
d	61	60	49	65	67	49
e	43	48	47	68	62	62
f	65	118	97	77	76	60

TABLE 4
INDIVIDUAL PATTERNS OF MOVEMENT OF THE BLOOD SUGAR (mg. %) IN 17 INFANTS BORN TO DIABETIC WOMEN FROM BIRTH TO 6 HOURS

Case	Hours					
	B	½	1	2	4	6
70	50, 51	23, 25	20·5, 21·5	17·5, 18·5	42, 44	59, 60
59	56, 55·5	42, 42·5	35, 35	57, 57·5	86·5, 85·5	70, 69·5
60	51, 51	38·5, 39·5	44·5, 44·5	34, 31	85, 81	91·5, 91
63	49·5, 50	23, 23	17, 18	23·5, 22·5	33, 31	39
64	112, 112	74, 75	46, 45·5	39·5, 38·5	74, 73	67, 67
69	61, 63	59, 61	54·5, 53·3	48, 48	78·5, 79·5	74·5, 73
65	76, 78	29, 30	21·5, 20	24·5, 25	54·5, 52·5	66, 65
71	91, 92·5	43, 43	27·5, 28	25, 23	36, 37	60·5, 58·5
72	52, 53	35·5, 35·5	29·5, 31	37, 37	53, 53	53, 53·5
73	48, 46·5	34·5, 35	39, 38	58·5, 58	76·5, 76·5	66, 66
74	55·5, 57	26·5, 25·5	20·5, 19·5	27·5	50, 51·5	45·5, 45·5
75	61	18, 20	14·5, 16	40, 34·5	42, 46·5	42·5, 40·5
83	72, 72	57	42·5, 41	22, 26	57·5, 59·5	68, 70·5
84	149, 144	97, 96	62, 60	21, 21·5	21, 21	36, 37·5
85a	63, 61	55, 53·5	44·5, 44	48, 48	66, 67	81, 81·5
85b	56, 58	40, 40	33, 33	42, 40·5	72·5, 74	76, 77·5
88	52, 50	68, 68	65, 66·5	60, 60	52, 52	53·5, 51
Mean ..	68	45·13	36·24	36·53	57·78	61·63
S.D. ..	25·6	20·3	14·8	13·4	18·4	14·9

TABLE 5

INDIVIDUAL PATTERNS OF MOVEMENT OF THE BLOOD SUGAR (mg. %) IN 16 INFANTS BORN TO DIABETIC WOMEN FROM SECOND TO TENTH DAYS

Case	Days								
	2	3	4	5	6	7	8	9	10
70	73·5, 76·5	59·5, 60·5	53, 55	61·5, 63·5	71, 72	72, 73	72·5, 75·5	75, 75	83, 84
59	67·5	63, 63·5	67·5, 67·5	73·5	77, 79	68·5	77, 74		
60	76, 75	80	73·5, 72·5	72, 69	82, 82	82·5, 81	80, 81	76·5, 76·5	87·5, 89
63	23·5, 22·5	28, 30	67·5, 65·5	74, 76	—	67, 68	66·5, 66·5	71·5, 74	75, 75
64	51·5, 50	58, 60	55·5, 56·5	82·5, 84·5	67·5, 67·5	73, 70·5	78, 75	74, 74	73, 75·5
69	59·5	48, 48	43, 43	60, 61·5	61·5, 62	72, 74·5	72, 73	72, 73	78, 75
65	46, 45	53·5, 53·5	50·5, 50·5	52, 50	63	68	74·5, 72	73·5, 75·5	78, 79
71	60·5, 59·5	46·5, 46·5	63·5, 66	74, 76	74·5	73·5, 75	78, 78	68, 68	69·5, 70
72	58, 55	66, 66	59, 59·5	63, 63·5	84, 84	72, 74	89·5, 91·5	80·5, 84	86, 88·5
73	65, 63	69, 69	71·5	72·5, 74	72·5, 76	76, 76	77, 79	81, 83	84, 85·5
74	33, 33·5	46·5	48, 49·5	66, 66	78, 79	79, 77	82, 84	79, 78	83, 83
75	19·5, 20·5	34·5, 34	34·5, 35	41, 40·5	44·5, 43·5	62·5, 62·5	74, 76	82	83·5, 84
83	53·5, 55	49, 50	36, 36·5	64, 66·5	72·5, 74	73, 74	68·5, 79·5	81, 77·5	81, 82
84	Died at 16 hours								
85a	63, 65	48, 48	71, 69	51, 53	61·5	76·5, 77·5	75, 83	69, 70·5	90·5, 92·5
85b	53·5, 53·5	41	47·5, 49·5	46·5, 43·5	66·5, 68·5	76·5, 74·5	75·5, 75·5	73, 73	72, 72
88	48	59, 60	44·5, 45·5	63·5, 65	67, 70	65, 66·5	71, 73	74·5, 76·5	76·5, 79·5
Mean ..	53·14	53·31	55·58	63·81	69·98	72·42	76·48	75·7	80·48
S.D. ..	12	12·7	12·1	11·4	9·7	4·8	5·2	4·2	6·1

The difference in the behaviour of the two groups, taken as a whole, is fairly accurately reflected in the arithmetic means of the groups at each time interval (Fig. 1).

Having demonstrated the dissimilarity of these two groups and the fact that the blood sugar level of the infants born to diabetic women reached its lowest point at one to two hours after birth, it was then possible to examine the behaviour of such infants in the whole series for whom serial blood sugar values in the first few hours of life were available. The value at birth was plotted graphically against the lowest level at 1 to 3 hours and the point was marked with a symbol signifying the nature of the clinical course (Fig. 2). The segment of the circle is divided into three sections in the uppermost of which lie points which signify that a fall occurred in excess of 50% of the birth level. In the central section lie points where a fall occurred which was less than 50% of the birth level and in the lowest section lie the points where the blood sugar actually rose after birth (probably in response to administered glucose).

The deaths are fairly evenly spread, but there are only five for whom figures are available, and of these only three babies were abnormal in the first few hours. The two infants who were asymptomatic in the period of lowest blood sugar are located in the topmost section, whereas of the three who were symptomatic in the first few hours, two are in the

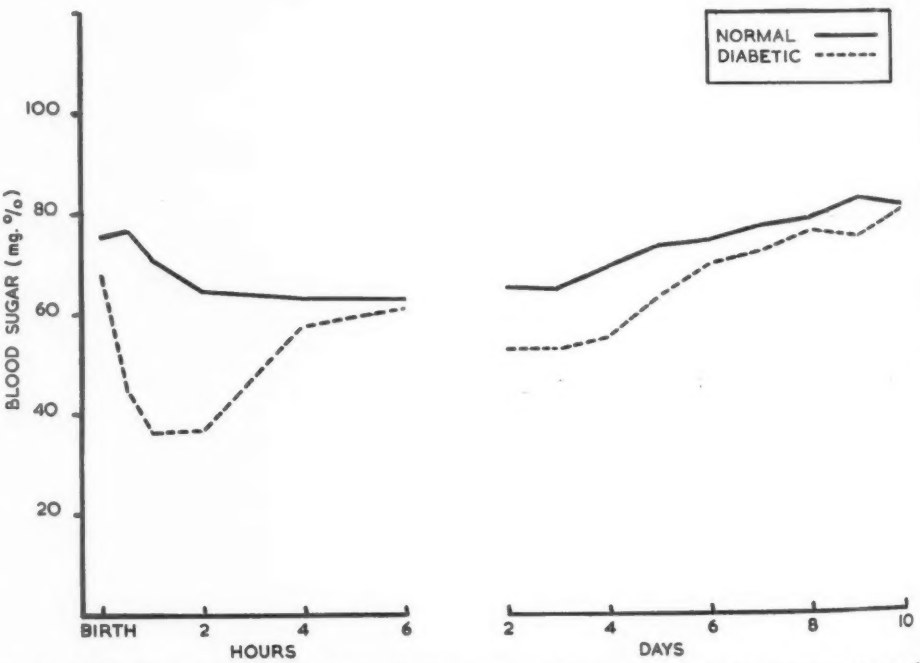

FIG. 1.—Arithmetic means of the blood sugar levels in a group of normal infants and in a group of infants of diabetic women.

TABLE 6

NECROPSY FINDINGS IN NEONATAL DEATHS OF INFANTS OF DIABETIC WOMEN

Case	Necropsy Findings
9	Pneumonia Terminal inhalation
18	Massive adrenal haemorrhage
32	Hyaline membrane
35	Intracranial haemorrhage Prematurity (1,644 g., 30 wk.)
40	Asphyxia
84	Massive cerebral haemorrhage Hyaline membrane
90b	Atelectasis
Twin 2	Prematurity (850 g., 30 wk.)
98	Renal thrombosis

centre of the middle section and one is in the lowest section.

Only 10 of the 54 infants represented on this graph were symptomatic in the first few hours when the trough of hypoglycaemia is normally attained. Three of the 10 died (Case 18 at 3 days, Case 32 at 11 hours and Case 40 at 4 hours) and none of them feature in the top section; two are in the middle section and there is one in the lowest. In two of the 10 symptomatic infants (Cases 3 and 6) the respiratory difficulties were undoubtedly the result of inhaling orally administered glucose. One other infant (Case 37) who is represented in the top section was apnoeic for some minutes after his initial cry, but he was perfectly normal at the time when his lowest blood sugar level was recorded. One (Case 69) had no significant fall in the blood sugar level (62 to 48 mg. %) while another (Case 46) showed a rise from 53 mg. % to 62 mg. %. One (Case 1) falls clearly into the topmost section and the last of the 10 (Case 19) also does so but the initial level of 522 mg. % certainly does not represent accurately the birth level of blood sugar as there were some minutes of delay in obtaining the specimen and the infant had been given 2 g. of glucose into the umbilical vein on delivery. Of these 10 infants, therefore, who were symptomatic when the maximum fall in blood sugar was to be expected, only three fall into the topmost section and of these one was asymptomatic at the most hypoglycaemic point, while in another the sugar level at birth did not represent the true facts. There are 17 infants in the topmost section of the segment, so that at least 15 of these were asymptomatic at the time interval during which the blood sugar of these infants is normally at its lowest. The symptoms presented beyond the first few hours in the remaining 44 infants bear no relationship to the change on blood sugar immediately after birth and occurred at a time when the sugar level had become stabilized.

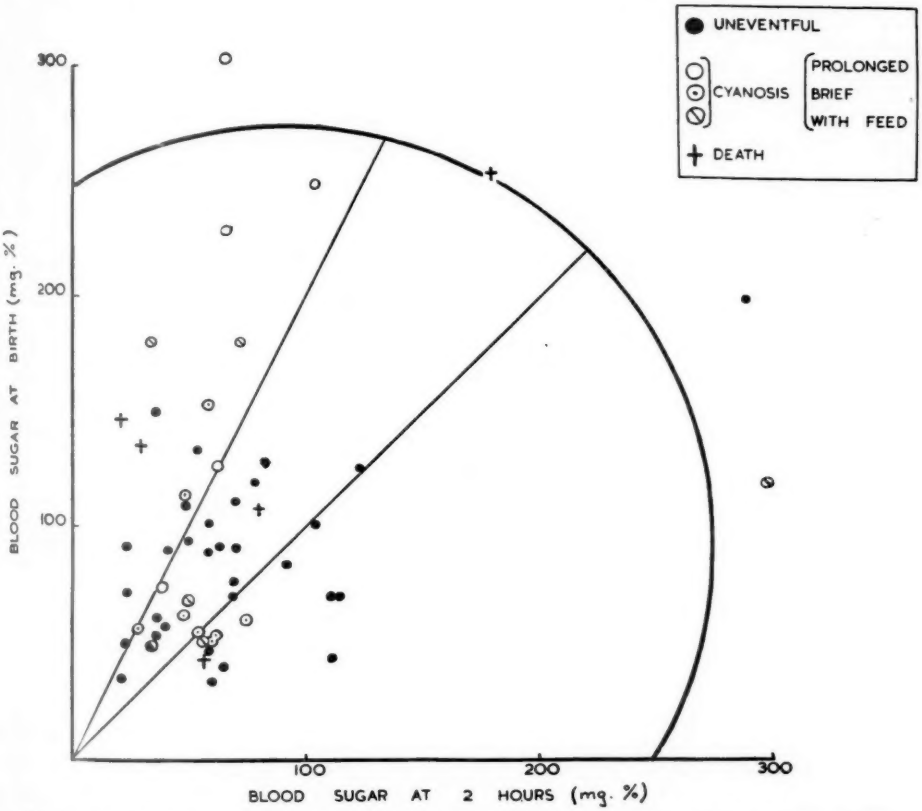

FIG. 2.—Relationship between blood sugar levels at birth and at 2 hours in infants of diabetic women.

In the series of 90 live born infants there have been eight neonatal deaths. With one exception these have been among the lighter infants. Very adequate cause for death has been found in seven at necropsy and in the eighth (Case 40, whose blood sugar rose from birth) the clinical and patho-

logical picture was of anoxia, although its cause was not determined. The important pathological findings are given in Table 5 and in addition the pancreas of each baby was found to have very definite hyperplasia of the islets of Langerhans. In Cases 18, 35, 40, 84, 90b and 98, either serial blood sugar levels or one preceding death are available and in none was hypoglycaemia present. Case 9 was a preventable death from neonatal pneumonia on day 9, and Case 32 (whose blood sugar underwent a minimal fall) presented signs of respiratory embarrassment immediately after birth and went on to die of pulmonary hyaline membrane at 11 hours.

Discussion

Before 1937 sporadic reports concerning a few infants born to diabetic women showed that these babies had blood sugar levels soon after birth which were abnormally low when judged by adult standards. In that year the much more thorough investigation of Hartmann and Jaudon demonstrated the fact that the normal infants of non-diabetic women had lower sugar levels in the blood than the adult but that even more hypoglycaemic levels existed in the offspring of diabetics. Fuller studies of the blood sugar in the normal newborn followed, and Farquhar (1954) added a further group in which the levels were determined repeatedly in the first six hours and daily thereafter. The analyses were carried through in duplicate by a suitable method and the specimens which were taken after the first day always followed an eight-hour fast, an omission which had cast some doubt on the value of previous investigations. From this and the preceding papers it was confirmed that the newly born infant might normally possess a low blood sugar level and that he might do so without showing any sign of clinical disturbance.

Miller and Ross (1940) carried out a small number of blood sugar determinations by the micro-method of Somogyi in the first 48 hours of life in premature and full-term infants of non-diabetics and in the infants of diabetic women. The last group had blood sugar levels similar to the prematures but significantly lower than the mature normals. It is not clear whether glucose was given to any of these infants or not. Reis, DeCosta and Allweiss (1950) compared the blood sugar levels of infants of normal women with those born to diabetic mothers. They employed the Somogyi modification of the Shaffer-Hartman micro-method, but they did not state its accuracy in their hands or the length of fast before blood was withdrawn. They do not give individual figures for the infants but the 'diabetic group' as a whole shows lower levels than the normal in the first two hours. Beyond that period few of the abnormal group had the level determined. They state that 'the blood sugar of babies born of diabetic mothers falls more rapidly during the first hour of life, falls lower, and returns to normal more slowly'. Komrower (1954) used a modified Folin and Wu micro-method in his study of normal infants and those of diabetic women. Duplicate determinations were made 'as often as possible', but the accuracy in his hands was not stated. The groups were studied in the important first 24 hours of life but not beyond this. Again it was shown that the infants of diabetics 'revealed a rapid drop in the first hours of life with a slow rise towards the end of the first 24 hours'. Pedersen (1952), and Pedersen, Bojsen-Møller and Poulsen (1954), on the other hand, who have carried out a great deal of very careful work on the subject of the diabetic pregnancy, employed the Hagedorn-Jensen method (the determinations were done by 'two experienced technicians' for the most part), but do not appear to have examined duplicate specimens. The accuracy of the method was repeatedly checked against glucose standards and 'the maximum deviation from the true value did not exceed 5%'. His figures are at variance with the others quoted for he was unable to demonstrate any difference in the blood sugar patterns of the normal and abnormal groups. The present study, however, shows that there is indeed a more profound and more rapid fall in the blood sugar levels of the infants of diabetic women, but that this is corrected spontaneously by six hours after delivery. By the second day the diabetic group again shows significantly low sugar values, but this gap is narrowed and becomes insignificant when feeding of the abnormal group gets under way on days five or six.

With the important exception of the results of Pedersen *et al.*, therefore, it appears to be agreed that these infants show a profound drop in the first few hours. There is less agreement about when stabilization occurs, but the experience of this study has shown fairly consistent correction by six hours. Farquhar (1954) has reviewed the theories about control of the blood sugar level in the neonatal period. Although some authors have sought to incriminate hepatic immaturity in the aetiology of neonatal hypoglycaemia there is little to suggest it. On the other hand, the neonatal adrenal cortex is undergoing remarkable involution in the first week and, in the infant of the diabetic, the pancreatic islets are usually hyperplastic. The latter observation was made first by Dubreuil and Anderodias (1920) and more than 20 papers followed it, including the excellent study of the morphology of infants of

diabetic pregnancies by Cardell (1953). It seems likely that there is an absolute increase in islet tissue in these infants and it has been the general opinion that this is due to an increase in the beta cells. If indeed there is an abnormally high output of insulin in these infants then a rapid fall in the blood sugar level immediately following birth would be expected. White (1949) was opposed to the theory of an absolute hyperinsulinism on the basis that the blood sugar level should then fall to zero, but this would be the case only if the pancreas continued to secrete insulin in the presence of hypoglycaemia and if there were no opposing mechanism such as the adrenal cortex. Pedersen (1952) and Pedersen *et al.* (1954) believed that the blood sugar level in the mother dictated the foetal liver threshold for glucose by determining the foetal output of insulin. Thus hyperglycaemia in the mother would stimulate foetal insulin production and the hepatic threshold would be low so that the blood sugar level in the infant would fall from a high birth level to the low liver threshold level after birth. This would mean that lower maternal levels would result in higher levels in the newborn and so the fall after birth would not be excessive. This is the explanation offered by Pedersen to explain why his group of abnormal infants did not differ in its blood sugar pattern from the normal group. Every effort was made to keep the mother's blood sugar within normal limits. Careful diabetic control was maintained in the women of this series by Dr. C. F. Rolland and yet the blood sugar of the infants fell profoundly and quickly. The spontaneous rebound in this study to a figure approaching the birth value indicates the presence of an adequately functioning mechanism opposing insulin. The facts would appear to be compatible with a state of increased insulin production which rapidly reverts to normal when the stimulus to production is withdrawn and/or when it is opposed by diabetogenic hormones from the adrenal cortex, chromaffin tissue or the pancreas itself.

It is clear, therefore, that the infants of diabetic women may have very low blood sugar levels in the hours after birth and also that they may have a variety of symptoms which may be classified roughly as respiratory, but it remains to be shown whether or not any relationship exists between these two findings.

Hartmann and Jaudon (1937) were of the opinion that cyanosis, irritability, listlessness, hypotonicity, hypertonicity, twitchings and even death might result from hypoglycaemia. They stated 'there can be no question, however, of the greater tendency in the abnormal (diabetic) group to develop extreme grades of hypoglycaemia with clinical manifestations severe enough to be fatal or so alarming as to require constant watching and sometimes frequent treatment to raise low blood sugar levels'. Miller and Ross (1940) noted symptoms in three of six infants and although the infants were biochemically hypoglycaemic they noted other abnormalities in the babies; congestive failure in two and possible birth injury or erythroblastosis foetalis in another. They noted a lag in the response of the infants to glucose, but felt this was analogous to the delayed response of a hypoglycaemic non-diabetic adult to glucose. Reis *et al.* (1950) enumerated the dangers to which these newborn infants were exposed and included hypoglycaemia without giving their reasons. John (1950) stated that the physiological hypoglycaemia of healthy newborn infants was benign and unproductive of symptoms, but that the hypoglycaemia which the offspring of diabetic women developed was malignant, leading to shock and to death unless it were treated early and energetically. Komrower (1954) in a comprehensive study observed signs which were considered to be suggestive of hypoglycaemia in four of 40 such infants whose blood sugar levels had been followed carefully from birth. In three the levels were less than 20 mg. % and the fourth baby had been subjected to a large and very rapid drop in blood sugar. On the other hand, Komrower found three infants who were symptom free with sugar levels of 20 mg. % or less. There is, however, some individual variation in the response of adults to hypoglycaemia and the epileptic in particular may respond with convulsions to a blood sugar level which would be responsible for milder symptoms only in a normal person. All of the deaths in Komrower's series appeared to be explicable on the basis of the pathological findings, without his requiring to incriminate hypoglycaemia. In 11 of 27 infants born to diabetic and prediabetic women, Reardon, Field and Baumann (1955) determined the blood sugar value at 4 hours. Seven of these had values of less than 15 mg. % and four of them died. Referring to the low blood sugar levels attained by normal infants of non-diabetic women, Donald (1956) stated 'the sharp change may well tax the child's endurance and metabolic resources overwhelmingly'. Pedersen (1952), whose work is the exception to the finding that infants of diabetic women have a more profound and more rapid fall in blood sugar, discovered no clinical evidence of hypoglycaemia in his group. Such abnormalities as did present in the first 24 hours of life were attributed to intracranial haemorrhage in one (diagnosed by cranial puncture), congenital heart disease in one (diagnosed by auscultation and

radiography), widespread atelectasis in two (diagnosed by auscultation and necropsy in one and by auscultation and radiography in another) and probable atelectasis in the fifth in which the diagnosis could not be verified. He did not note the blood sugar to be abnormal in the presence of cyanosis in these babies.

Those obstetricians and paediatricians who have feared the effects of hypoglycaemia upon the infants of diabetics have suspected that, although such low levels may not be productive of symptoms at the exact moment when the trough of hypoglycaemia was reached, nevertheless the structure and the function of, for example, the brain, the heart, the lungs, or the vessels might have been so altered by it that symptoms might develop later, even after the blood sugar had been somewhat restored. These are very hypothetical considerations, but they are possible and they must receive an answer.

It is believed that this study has confirmed that the blood sugar falls further and more rapidly in the infants of diabetic women than in those of normal women. It has also been shown that the infants in the 'diabetic' group may have blood sugar levels which may be described as low or normal or high in the presence of 'respiratory' incidents and that there is no relationship between these incidents and the blood sugar level at that time. It has also been shown that there is no relationship between the magnitude and speed of the fall in blood sugar and the development of abnormal signs in the babies. Finally it is believed that it has been shown that there is no relationship between the magnitude and/or the speed of the fall in blood sugar and the development of abnormal incidents later in the first two weeks of life.

Following the completion of this investigation an attempt has been made to examine all the surviving children as a logical sequel to the previous work in order to exclude the possibility of hypoglycaemia having caused cerebral damage which had passed unrecognized at the time. Of the 90 infants born, 82 survived the newborn period. One of these (Case 30) died suddenly at home at the age of 1 month. His neonatal course in hospital was quite uneventful. The blood sugar fell from a birth level of 94 mg. % to 72 mg. % at 1 hour and 50 mg. % at 3 hours from which point it rose steadily. Death was sudden and was associated with aspiration of a feed. His doctor heard a cardiac murmur for the first time just before the baby died and on this evidence alone certified death as having been due to congenital disease of the heart. There was no necropsy. Another infant (Case 3), whose neonatal course was complicated by inhalational incidents, but whose blood sugar was never abnormal, developed very severe meningococcal meningitis complicated by cerebral venous thrombosis at 2 months and suffers from secondary amentia.

Of the remaining 80, all but five (three of whom have emigrated) have been traced and their present health assessed. Of the 75 children I have examined 69 personally; three have been examined for me by other physicians; the mothers have supplied detailed information by correspondence in two cases (one in the north of Scotland and one in Aden) and information was supplied about the remaining case by a children's officer.

From these various sources it can be said that 71 of the children are apparently normal in intelligence and behaviour. One (Case 42) has been in hospital since 1953 when at 3 years of age she developed Perthe's disease of the hip. The physician thought that at 5 years of age the child was a little backward, but it has not been possible to see her personally to assess how much of her retardation may be attributed to prolonged institutional care. The infant certainly had a normal neonatal course and was not hypoglycaemic at any point. Two children are certainly mentally defective, one being a mongol and the other is the surviving dizygous twin (Case 90a). The latter infant weighed only 1,021 g. at birth, and although he had a rather low blood sugar level initially, it rose spontaneously and he was in good condition in the newborn period. He also suffers from retrolental fibroplasia.

Finally, Case 63 is a small boy who is undoubtedly dull, but whose home background is very bad. The mother was a prostitute, she was very unstable emotionally and she did not care for her children. She died while attempting to induce the miscarriage of a further pregnancy when the patient was only a few months old. The father, who is an unstable and violent man and whose intelligence may be subnormal, married again, but with no advantage to the family. The child has grown up unloved, without proper care and is backward and dirty at the age of 2½ years. Although his blood sugar level did in fact fall by over 50% in the first hour of life, and although it remained below 30 mg. % on days two and three, he was quite asymptomatic throughout the neonatal period. Case 75, whose blood sugar fell by more than 75% in the first hour, and in whom it was 20 mg. % on day two, and in whom the level did not exceed 40 mg. % until day five, is at the same age a very normal little girl. It seems much more likely that the backwardness in Cases 90a and 63 is the result of factors other than the hypoglycaemia.

Hartmann and Jaudon (1937) recommended that

the hypoglycaemia of these babies should be prevented by the very early institution of regular carbohydrate and milk feeds and that where symptoms developed the babies should have epinephrine and dextrose parenterally. Reis *et al.* (1950) recommended that a 50% glucose solution should be given orally by medicine dropper in the first hour of life and that after the first two hours the infant should receive ½ to 1 oz. feeds two hourly of breast milk, and 5% glucose alternately during the first day of life. Whitely, Adams and Parrott (1953) recommended the subcutaneous administration of glucose to the newly born infant. Drury (1953) also recommended its parenteral administration. Komrower (1954) studied two groups one of which received no glucose, whereas the infants of the other received 2 g. glucose by mouth as a 50% solution in the first eight hours of life. There was no significant difference in the blood sugar levels of the two groups, and Komrower, therefore, decided to give glucose only when symptoms attributable to hypoglycaemia developed. Pedersen (1952, 1954) saw no point in using glucose at all. The results of this investigation make it clear that there is no need to use glucose in the infants of diabetic women. Its oral administration is accompanied by a very real risk of vomiting and inhalation, while the parenteral administration of isotonic solutions subcutaneously or intravenously only serve to increase the abnormal volume of the body water. The intravenous use of hypertonic solutions may embarrass the heart by increasing the intravascular fluid volume. From 1948 to 1951 we used 20% to 50% solutions intramuscularly without complication. The present policy is in line with that of Pedersen (1952; Pedersen *et al.*, 1954) and it is felt that not only is the use of glucose unnecessary, but it may hinder the establishment of the correct diagnosis by its suggesting that hypoglycaemia is the responsible factor.

Finally the investigation provides support for the policy adopted fully in Edinburgh by 1952 that all fluid should be withheld until the fourth or fifth day of life.

Summary

Confirmatory evidence is offered that the blood sugar level falls more profoundly and more rapidly in the infant of the diabetic mother than in the offspring of the normal woman. It is shown that there is no relationship between the development of a morbid neonatal course and the blood sugar level at the time or the extent and rapidity of the fall. It is shown also that there is no relationship between the degree of hypoglycaemia or the gradient of the change in levels and abnormal incidents later in the first two weeks of life. It is probable that there is no relationship between the blood sugar changes and subnormal intelligence in later childhood.

The administration of glucose may be dangerous and at the least it may serve to postpone the establishment of the correct diagnosis in abnormal infants.

I wish to express my gratitude to Professor R. W. B. Ellis for his encouragement and advice, the nursing staff of the Simpson Memorial Maternity Pavilion for their cooperation, Miss D. Trench of the Royal Edinburgh Hospital for Sick Children and the children's departments of various local authorities for extensive assistance in tracing the present whereabouts of the children and their parents, who have been generous in their help.

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THE EFFECT OF LARGE DOSES OF 'SYNKAVIT' IN THE NEWBORN

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Experimental work during the years 1929 to 1934 established the fact that a haemorrhagic disease observed in chicks was due to deficiency of a fat-soluble dietary factor: in 1935 Dam proposed the name vitamin K (Koagulations vitamin) for this factor. Dam, Schønheyder and Tage-Hansen in 1936 demonstrated a hypoprothrombinaemia which prolonged the clotting time in vitamin-K-deficient chicks, although vitamin K itself had no thrombin-like activity. In 1935 it was shown that mammals might develop vitamin K deficiency with its associated hypoprothrombinaemia and haemorrhagic tendency. Warner, Brinkhous and Smith described the syndrome in human adults in 1938, relating it to destructive jaundice: meanwhile, haemorrhagic disease of the newborn with hypoprothrombinaemia had been observed in 1937 by Brinkhous, Smith and Warner.

Treatment with vitamin K has now become an established form in haemorrhagic disease of the newborn and its effect on the prothrombin time is widely recognized. Waddell and Guerry found that the period of most marked prothrombin deficiency occurred from 48 to 72 hours after birth, and drew attention to the apparent seasonal variation in prothrombin deficiency, which is most marked in winter and maximal in March judged by the incidence of deaths due to haemorrhagic disease (Waddell and Guerry, 1939a and b; Waddell, Guerry and Birdsong, 1940; Waddell, Guerry, Bray and Kelley, 1939; Waddell and Lawson, 1940).

It has become the general practice in maternity units to administer a routine prophylactic dose of vitamin K to all infants at birth.

Physiology of Vitamin K

As far as is known, vitamin K has only one function in the body. It is essential for the synthesis of prothrombin by the liver. Vitamin K participates in the enzyme system in the liver, producing prothrombin, but is not itself part of that glycoprotein.

Natural fat-soluble vitamin K requires bile salts for its absorption from the gastro-intestinal tract but the synthetic water-soluble analogues do not. Vitamin K is produced by bacteria in the small bowel which synthesize sufficient to cover normal daily requirements. The human requirements of vitamin K are not known, but Hardwicke (1944) has estimated that 0·5 to 5 μg. daily are sufficient to prevent hypoprothrombinaemia in the newborn. Dam has shown that human milk contains little or no vitamin K. A small but definite amount of vitamin K can be stored in the liver (Lord, Andrus and Moore, 1940) and any excess is excreted in the stool.

Toxic Effects of Vitamin K

Until recently no toxic effects had been observed clinically from the administration of vitamin K and its analogues. Experimentally, massive doses of the vitamin were given to mice by Molitor and Robinson in 1940 and by Ansbacher, Corwin and Thomas in 1942, and both groups noted injury to the circulating blood cells, while Smith, Ivy and Foster in 1943 remarked on the production of an aplastic anaemia in experimental animals after massive doses of vitamin K. Respiratory depression and 'acute vascular congestion' are also mentioned as toxic effects. Very recently, the effect of vitamin K on the red cells has been emphasized by Allison (1955) who noted increased haemolysis in newborn premature infants given large doses. Moore and Sharman (1955) produced haemoglobinaemia in vitamin E-deficient rats with massive doses of vitamin K. About the same time, Laurance (1955) observed a remarkable increase in the incidence of kernikterus in premature babies following an increase in the routine dosage of vitamin K. In a retrospective survey, Crosse, Meyer and Gerrard (1955) found that there had been a steadily increasing incidence of kernikterus of prematurity which could be related to an increasing dosage of vitamin K.

* Holding a scholarship from Cecil John Adams Foundation Trust.

All these findings tend to verify the suspicions raised by Gasser in 1953 who mentioned vitamin K as a possible cause of severe haemolytic anaemia in 14 premature babies.

Present Investigation

This was undertaken in order to compare the serum bilirubin levels of groups of babies (full-term and premature) who were given no vitamin K with comparable groups who were given vitamin K ('synkavit') intramuscularly.

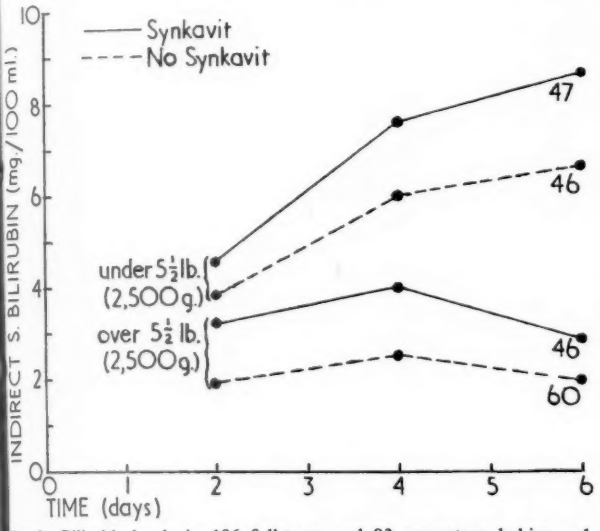

FIG. 1.—Bilirubin levels in 106 full-term and 93 premature babies with and without 'synkavit'.

The routine vitamin K dosage in the unit concerned was as follows:

(*a*) Full-term babies (over 5½ lb. or 2,500 g.) were given 10 mg. 'synkavit' intramuscularly at birth and no further dose.

(*b*) Premature babies (5½ lb. or 2,500 g. or less) were given daily doses of 10 mg. 'synkavit' intramuscularly until feeding was begun, and the average total dose received by the premature babies in the 'synkavit' group was 30 mg. The 'synkavit' group comprised 93 babies of all weight groups and the 'no-synkavit' group comprised 106 babies of all weight groups.

Blood samples were taken by syringe from the femoral vein on the second, fourth and sixth days of life. The blood was allowed to clot and retract for two to four hours at room temperature before being centrifuged and the serum taken off by pipette. The modification described by Malloy and Evelyn (1937) for the Van den Bergh reaction was used in the estimation of both direct- and indirect-reacting bilirubin. The former was not considered toxic and has been disregarded in this paper, the indirect reacting bilirubin only being given: in any case, the highest reading of direct-reacting pigment obtained was 3·4 mg., in a full-term baby.

Of the 199 babies included in the investigation, 106 were full term: 60 of those babies received no vitamin K and 46 each received a dose of 10 mg. 'synkavit' at birth. The remaining 93 were premature: 46 of those received no vitamin K and the remaining 47 received doses of 'synkavit' varying from 10 to 50 mg. (average 30 mg.). Fig. 1 shows the mean serum bilirubin levels in the 106 full-term and 93 premature babies.

There was a wide overlap of bilirubin readings of individual members of each group and the calculated standard deviation was large, but it is interesting to note that the mean levels of these babies who received no 'synkavit' (both full-term and premature) were so much lower than those who received a dose which had not been considered toxic.

The general increase in the mean bilirubin levels

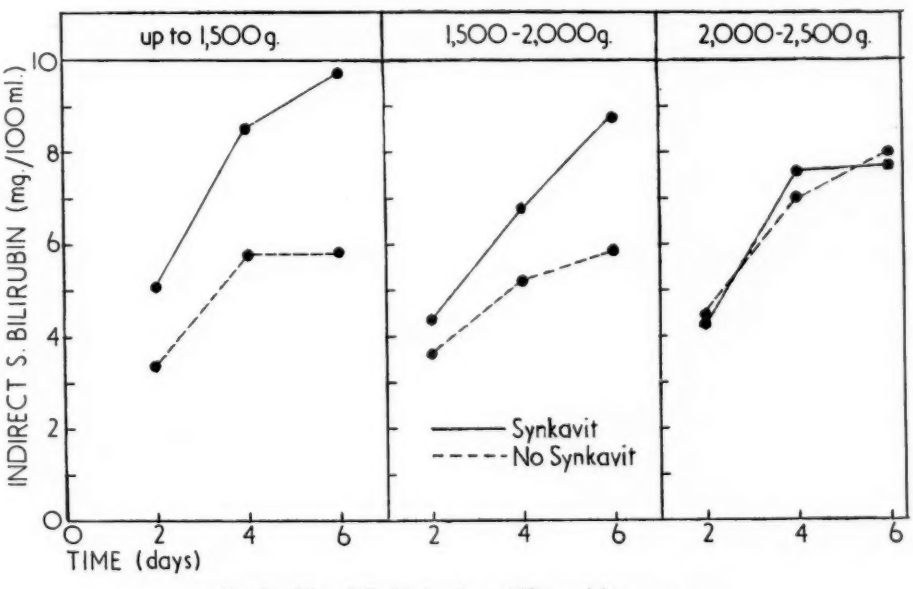

FIG. 2.—Mean bilirubin levels per 500 g. weight groups.

on the second, fourth and sixth days after the administration of 'synkavit' is still seen when different birth weight groups are studied separately, with the exception of a group weighing 2,000 to 2,500 g.: in this group there was little difference between the serum bilirubin levels of the babies given 'synkavit' and babies given none (Figs. 2 and 3). This is difficult to explain but Bound (1955) had a similar experience.

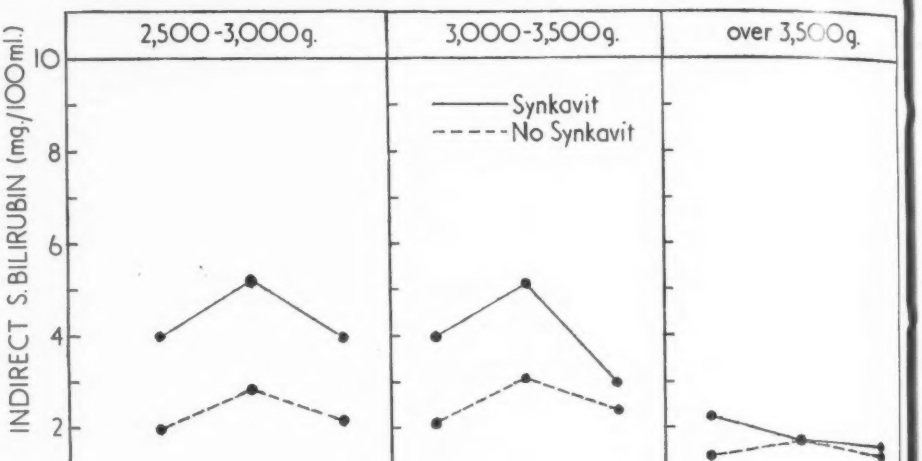

FIG. 3.—Mean bilirubin levels per 500 g. weight groups with and without 'synkavit.'

Discussion

Kernikterus of prematurity in the absence of iso-immunization is known to be related to the level of bilirubin in the infant's serum (Claireaux, Cole and Lathe, 1953; Crosse *et al.*, 1955; Meyer, 1956). There is little doubt that intramuscular 'synkavit' in large doses causes some elevation of the serum bilirubin levels of the newborn baby, whether full-term or premature. In the case of the premature baby, with poor liver function, the added effect of the 'synkavit' may just raise the serum bilirubin to a sufficiently high level to produce kernikterus. Table 1 (Crosse *et al.*, 1955) shows the incidence of kernikterus of prematurity compared with the dosage of 'synkavit' employed in the unit concerned in this investigation.

During this 10-year period, the average number of babies admitted has risen gradually from 200 per year to 300 per year: after the inception of the National Health Service in 1948 the percentage of small babies went up, but since 1950 there has been no change in the type of baby admitted and no major

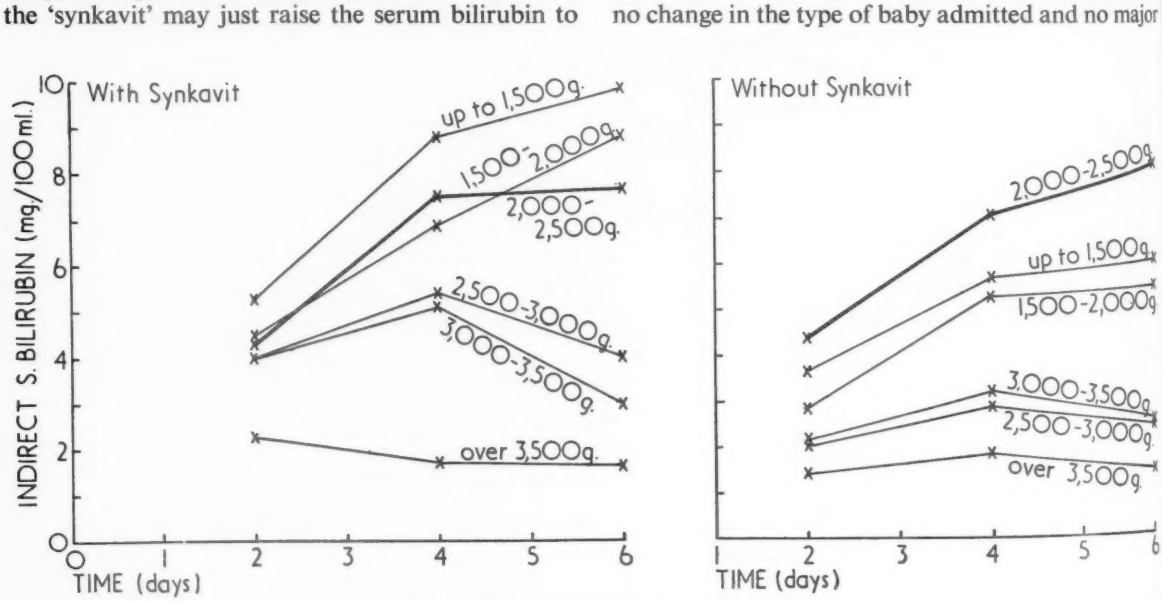

FIG. 4.—Mean bilirubin levels per 500 g. weight groups.

TABLE 1
INCIDENCE OF KERNIKTERUS OF PREMATURITY COMPARED WITH DOSAGE OF 'SYNKAVIT'

Year	Total Dosage of 'Synkavit' (mg.)	Percentage Developing Kernikterus
1945	1–2	0·9
1946		2·1
1947		0·8
1948		0·5
1949	10	1·6
1950		1·2
1951	30	1·1
1952		0·4
1953	More than 30	4·1
1954		3·6

change in the care of the babies other than the increased dosage of 'synkavit' to account for the severe rise in the incidence of kernikterus in 1953 and 1954.

The mode of action may be an increased haemolysis of red cells which would increase the circulatory bilirubin. It is, therefore, of interest to find that there was no significant difference in the percentage of babies requiring blood transfusion amongst the group receiving 'synkavit', when compared with those who received none (babies whose haemoglobin dropped to 60% or less were transfused), but this is a very rough method of assessing the degree of anaemia. It is possible that the action of large doses of 'synkavit' might be hepatotoxic rather than haemolytic or it might have both haemolytic and toxic actions.

The mean bilirubin curve of the babies in the 2,000-2,500 g. weight group shows a marked contrast to those of other weight groups. Without 'synkavit', the 2,000-2,500 g. curve is the highest, and this does not fit into the general picture in which the mean bilirubin levels decrease as the birth weight increases (Fig. 4). We have already shown that the mean bilirubin levels in this weight group are practically unaltered by the administration of 'synkavit' (Fig. 2). The fact that the estimations were done in the same laboratory under standard conditions seems to discount any experimental error but the sample is small and the scatter of individual results wide. It may be that at this stage of development (34-37 weeks) there is an alteration in the susceptibility of the red cell leading to increased haemolysis, or some change in the rate of conversion of bilirubin in the liver: these hypotheses do not, however, explain the absence of change when 'synkavit' is given compared with the change in the other weight groups.

Summary and Conclusions

The effect of large doses of 'synkavit' on the level of serum bilirubin in the first week of life is presented, and the possible mode of action is discussed. It is suggested that large intramuscular doses of 'synkavit' increase the risk of the development of kernikterus in premature babies by raising the already high level of serum bilirubin.

There is still a place for vitamin K in the prophylaxis and treatment of haemorrhagic disease but a dose of 1 to 2 mg. is sufficient.

Our thanks are due to Dr. V. Mary Crosse for her guidance, encouragement and criticism during the preparation of this paper; to Dr. A. H. Henly and his staff for technical assistance; to Mr. Holland for his help with the graphs; and the Matron, Sister Murray, sisters and staff of Sorrento Maternity Hospital, without whose helpful cooperation this investigation would not have been possible.

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CONGENITAL LOBAR EMPHYSEMA

BY

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Congenital lobar emphysema, though an established clinical entity, seems a relatively rare condition if judged by the small number of cases reported, particularly in this country (White-Jones and Temple, 1954; Belcher and Siddons, 1954). It is, however, likely that a more widespread knowledge of the clinical manifestations will reveal it as a not altogether uncommon disease of the very young.

Generally the affected infants present the picture of an acute respiratory emergency in the neonatal period or during the first few months of life. There is usually a history of recurrent attacks of dyspnoea and cyanosis which tend to increase in severity. Wheezing is often a marked feature of the condition, as well as recession of the intercostal spaces and indrawing of the suprasternal area. Examination suggests emphysema of one lung and radiological investigation shows the increased air content of one lobe, almost always an upper one, which herniates through the anterior mediastinum towards the opposite side. Early recognition and lobectomy may lead to complete recovery.

During the past five years three cases came under observation, each of them illustrating a particular and interesting facet of the problem and so warrant their recording.

Case Reports

Case 1. D.O., a boy, aged 4 months, was admitted to hospital on September 20, 1950, suffering from acute gastro-enteritis. There was a history of rapid respiration since birth with prominent movement of the alae nasi. Lying on the right side increased the dyspnoea and bulging of the anterior chest wall had also been noticed by his mother. On clinical examination there was indrawing of the suprasternal notch and lower ribs. There was no cyanosis. The chest was bulging centrally and there was hyperresonance with diminished air entry on the left side.

A chest radiograph (Fig. 1) showed extensive emphysema of the left upper lobe with marked mediastinal shift to the right. Compression had caused atelectasis of the left lower lobe and there was anterior mediastinal herniation of the emphysematous lobe.

As the baby's condition did not show any deterioration he was discharged from hospital and followed up as an out-patient. Clinical and radiological examination on January 19, 1951, revealed no change, but when the baby was seen again on August 28, 1951, although the clinical condition remained unaltered, radiological examination showed a definite decrease in the emphysema of the left upper lobe. He remained well and attended for further radiographs (Fig. 2) on February 29, 1952, which showed considerable improvement. The left upper lobe remained emphysematous but there was considerable reduction to the mediastinal shift and some re-expansion of the left lower lobe.

The patient re-attended on February 4, 1955, aged 5 years, for reassessment before beginning school. He appeared well developed for his age but the upper ribs were prominent with a depressed sternum. Physical examination of the chest showed hyperresonance of the

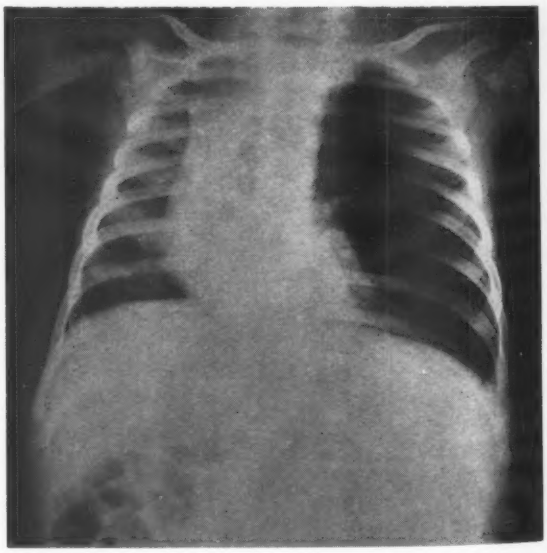

FIG. 1.—Case 1. Chest radiograph September 20, 1950, showing extensive emphysema of the left upper lobe with herniation to the right, marked mediastinal shift and compression atelectasis of the left lower lobe.

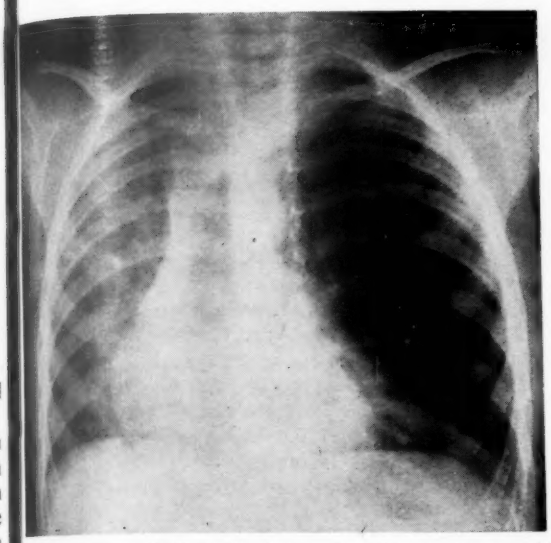

FIG. 2.—Case 1. Radiograph of the chest taken on February 29, 1952, showing reduction in the mediastinal shift and some re-expansion of the left lower lobe. The left upper lobe remains emphysematous.

left side with slightly diminished air entry. A few dry adventitious sounds were audible on either side of the sternum. His mother stated that his exercise tolerance had gradually improved and that he could walk and run quite easily without undue breathlessness. Two years previously he had had a severe attack of bronchitis which lasted eight months.

A radiograph of the chest (Fig. 3) showed only a small degree of emphysema of the left upper lobe and slight mediastinal shift to the right.

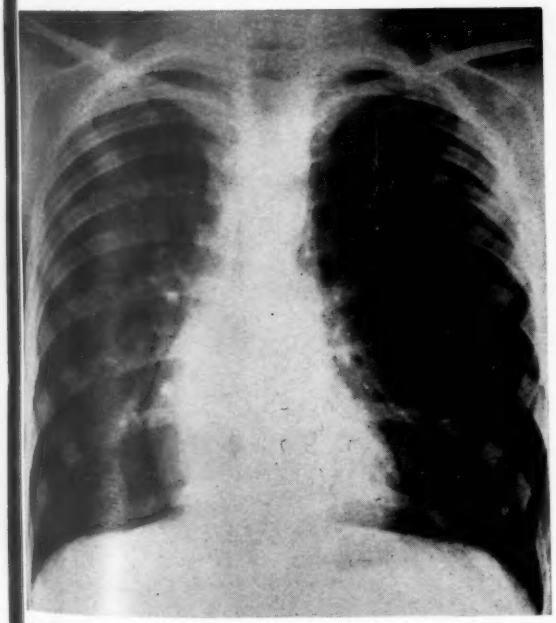

FIG. 3.—Case 1. Chest radiograph February 4, 1955, showing some emphysema still and a slight degree of mediastinal shift.

Case 2. Marguerite B. was born on June 14, 1953, at full term with a normal delivery at a large maternity hospital (birth weight 6 lb. 15 oz.). She was breast fed for eight days, then because of failing lactation put on a formula of half-cream National dried milk. Shortly after discharge from hospital her mother noticed that the baby was wheezy and short of breath. At the age of 4 weeks she had had several attacks of dyspnoea accompanied by what was thought to be colicky abdominal pain lasting about half an hour on each occasion.

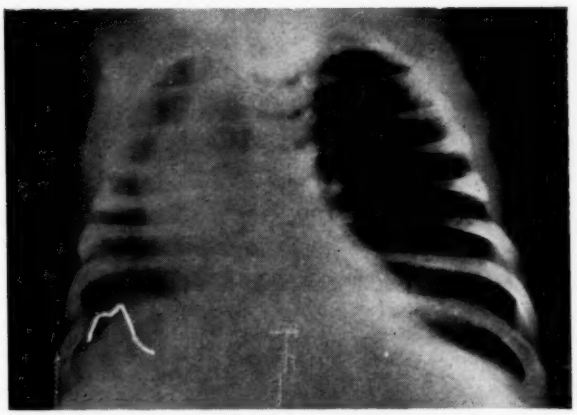

FIG. 4.—Case 2. Emphysema of the left upper lobe with herniation to the right. Considerable mediastinal shift to the right, atelectasis of the left lower lobe.

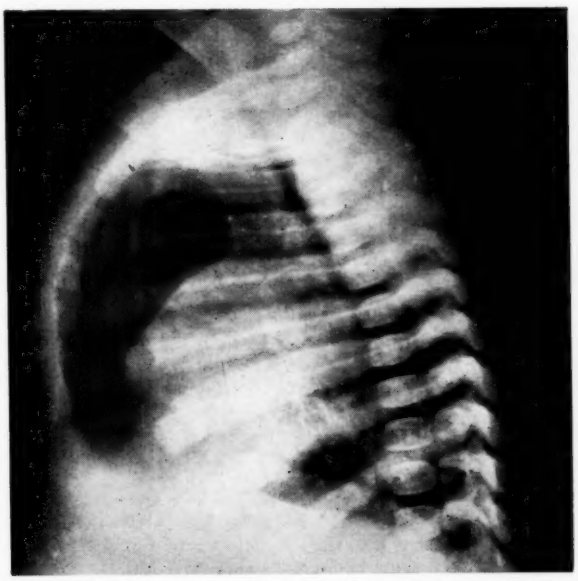

FIG. 5.—Case 2. Left lateral view, showing separation of the heart from the bulging anterior chest wall by the emphysematous lobe.

On July 30, 1953, she had several convulsions with twitching movements in the muscles of the face and left arm. Because of the persistence of the convulsions she was admitted to hospital on the same day.

The grandfather had asthma and the mother had

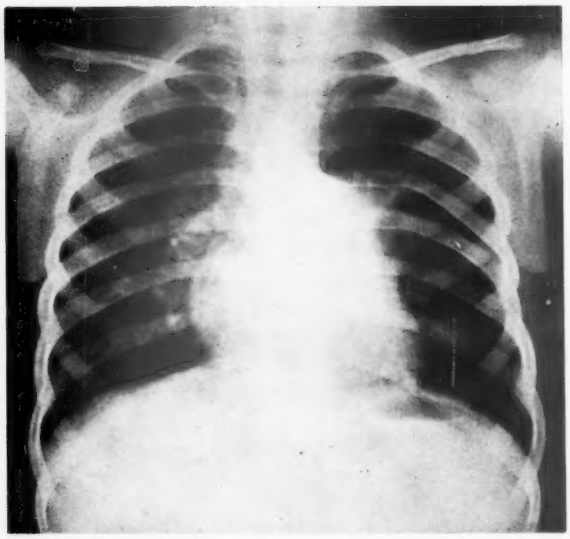

FIG. 6.—Case 2. Radiograph of chest 20 months after operation.

slight dermatitis of both hands, recurring every winter. She was suspected of having hyperthyroidism during the pregnancy.

Examination on admission showed an extremely pale, ill baby, cyanosed, very dyspnoeic and restless. There was marked wheezing, rib recession and indrawing of the suprasternal space. The percussion note over the left side of the chest was hyperresonant with greatly diminished air entry on the same side. The mediastinum was displaced to the right and the heart sounds could be heard more clearly on the right. The anterior chest wall appeared raised so that the chin practically rested on it.

A clinical diagnosis of tension pneumothorax was made and drainage under water immediately instituted, as the child's desperate condition did not allow radiological examination. Some improvement followed but no alteration in the mediastinal displacement. The thoracocentesis was stopped because of the development of subcutaneous emphysema.

Radiological examination showed an extensive obstructive emphysema of the left upper lobe with herniation to the right side through the upper part of the anterior mediastinum (Figs. 4 and 5). The baby's condition remained relatively stable, though she was still dyspnoeic, until August 14, 1953, when she suddenly collapsed, became extremely cyanosed and lost consciousness, but recovered again within 30 minutes. Because of repetition of the attacks she was bronchoscoped. Except for the deviation of the trachea no abnormality was detected.

On August 25, 1953, an exploratory thoracotomy was carried out on the left side (Mr. Dewsbury). The left upper lobe appeared grossly distended and uniformly emphysematous. The lower lobe was atelectatic and filled only a small space at the bottom of the chest cavity. The left upper lobe was resected easily. Postoperative convalescence was uneventful and she was discharged home on September 16, 1953.

Microscopical examination of the resected lobe showed only pathological changes compatible with the emphysema. The bronchus appeared normal.

The patient remained well until October 15, 1953, when she was re-admitted with signs of respiratory distress, cyanosis and marked wheezing. There were signs of upper respiratory tract infection. Despite antibiotic therapy her condition deteriorated and for the next six days she remained desperately ill; only subcutaneous injections of adrenaline relieved the respiratory distress. Following a course of cortisone she gradually recovered and was discharged home.

She was last seen in April, 1955, aged 23 months. Her general condition was excellent; she was lively, active, running about singing and had learnt to talk. A slight wheeze was audible on auscultation. In the intervening period she had had a number of attacks of varying degree of dyspnoea, always associated with wheezing and usually precipitated by a respiratory infection (Fig. 6).

Case 3. David A. was admitted to hospital on December 26, 1954, aged 11 weeks. The history was that he had been 'wheezy' since birth. Three days before admission he had developed a cough and had been noticed to become increasingly breathless.

On admission he was extremely dyspnoeic and slightly cyanosed. The anterior chest wall was raised to the level of the chin, and the chest was fixed in almost complete inspiration, respiration being mainly diaphragmatic. On auscultation there were rhonchi and fine crepitations throughout both lungs, and air entry over the left lung was markedly decreased. Radiographs of the chest on December 28, 1954 (Fig. 7) showed gross emphysema of the left upper lobe, with herniation across to the right and compression atelectasis of the left lower lobe.

He was treated with antibiotics and oxygen, and clinically his condition improved, but examination of the chest still showed hyperresonance and diminished

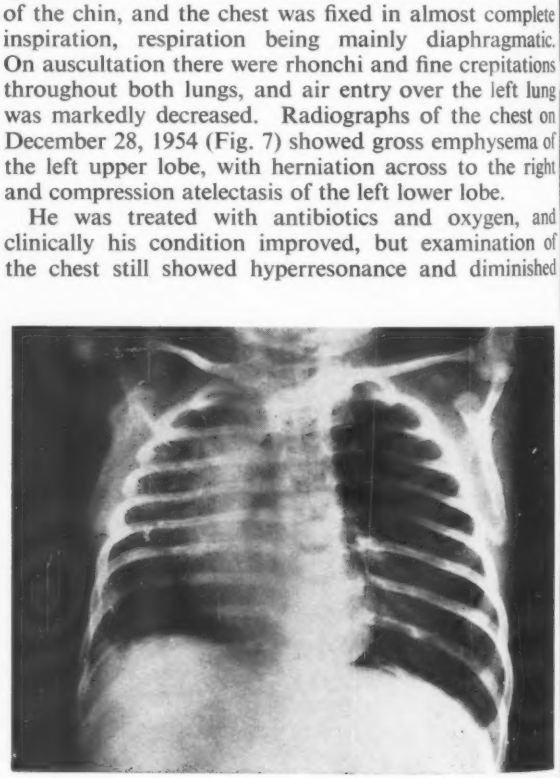

FIG. 7.—Case 3. Gross emphysema of the left upper lobe, herniation to the right, and atelectasis of the left lower lobe.

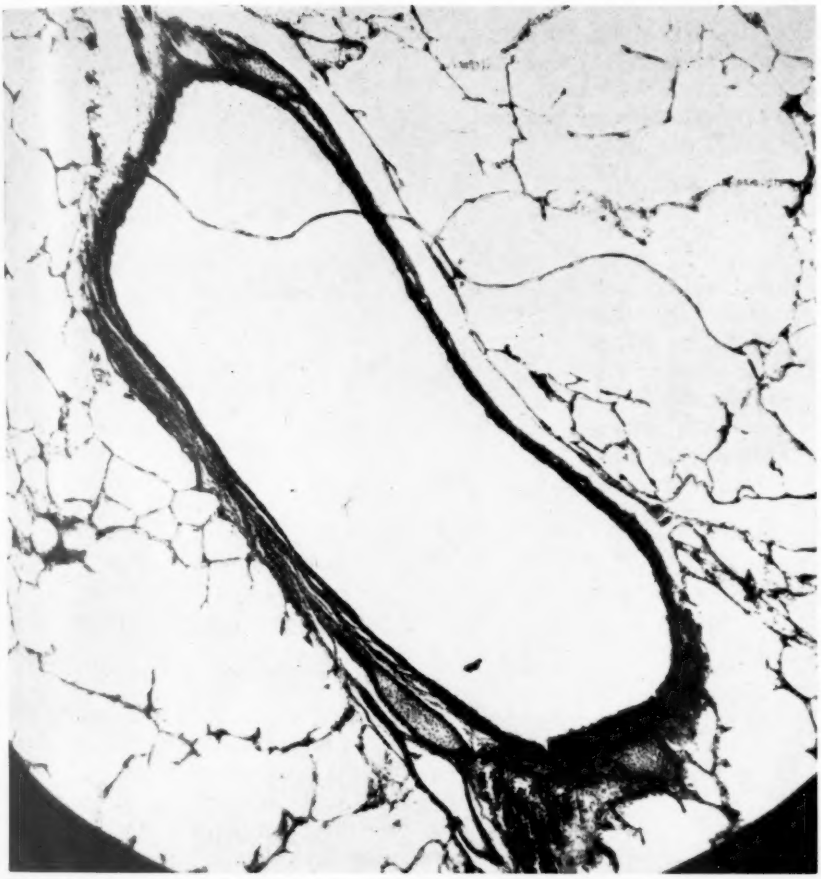

FIG. 8.—Case 3. Section of the left upper lobe showing only a very small amount of cartilage supporting a large bronchus and emphysematous changes in the parenchyma. ×50.

air entry throughout the left lung. Chest radiographs on January 3, 1955, and January 18, 1955, showed no change.

On February 14, 1955, left upper lobectomy was performed. At operation the left upper lobe was distended and had an unnatural spongy texture, but it was not entirely incompressible. The apical and dorsal segments were affected more severely than the lingular and anterior ones. The lower lobe was collapsed. There was nothing unusual about the lobectomy except that the upper lobe bronchus arose from the left main bronchus in two parts, one going to the apical and dorsal segments, and one to the anterior and lingular segments.

A section showed chronic emphysema. No cartilage was seen in the medium-sized bronchi examined, and only very small patches of cartilage tissue in different parts of the large bronchi (Figs. 8 and 9).

Post-operatively the child made an uninterrupted recovery.

Discussion

Our first case, although presenting the classical clinical and radiological picture, was not acutely distressed. No operation was performed. During the five-year observation period the clinical signs have regressed and the patient has developed normally. He successfully overcame a severe respiratory illness. Now his exercise tolerance is normal and the only residual physical signs are bulging of the chest, with some hyperresonance, and depression of the sternum (Fig. 10).

Two similar cases of spontaneous regression of lobar emphysema are reported by Caffey (1953). Both cases were diagnosed when 5 weeks old, and were observed for two years and three and a half years respectively. The right lung was affected in one, and the left lower lobe in the other. The latest chest radiographs showed only increased translucency of the affected lobes. The ultimate fate of these cases is not yet known but it is interesting to conjecture that unrecognized this disease may be the cause of 'unequal translucency of the lungs' presenting in adults, as described by Macleod (1954). Samson (1953) mentioned the case of a young man, aged 21 years, who was examined before an operation for pectus excavatum. The *x*-ray film of the lung showed poor markings and increased translucency on the right side. At thoracotomy the surgeon found an enormously distended emphysematous middle lobe filling practically the whole of the right chest cavity. A congenital origin was presumed. It seems therefore that the condition, contrary to general opinion, is compatible with survival without surgical intervention and may run a self-limited course.

Case 2 presented at the age of 6 weeks with convulsions indicating that the condition may lead to such a degree of anoxia as to cause loss of consciousness and convulsions which subsided when it was relieved by oxygen. Post-operatively she had an extremely stormy passage and although her condition appeared subsequently satisfactory, so far as her general development was concerned, she was never free of physical signs and wheezing has been a

marked feature from time to time. A few weeks after operation emphysema developed in the lower lobe on the same side. No definite anatomical lesions had been diagnosed to account for the development of emphysema in the upper lobe but as the condition spread post-operatively one may assume that there was some weakness of the cartilage of other bronchi on the same side.

Recurrence of respiratory symptoms post-operatively in all his patients was reported by Sloan (1953). Two of the four infants showed radiological evidence of emphysema in other portions of the lung following the lobectomy similar to this case. The explanation put forward was that the bronchial abnormality was not limited to the removed lobe. Interesting also is the fact that in one of the babies excellent temporary relief was obtained with subcutaneous injections of adrenaline, in the absence of any history of allergy in the child or his family, an experience not unlike our own.

Among reported cases absence or hypoplasia of bronchial cartilage has been described by Shaw (1952) in two cases, and by Fischer, Potts and Holinger (1952) in one out of six cases. In Case 3 a similar anatomical lesion was found which explained the development of the emphysema.

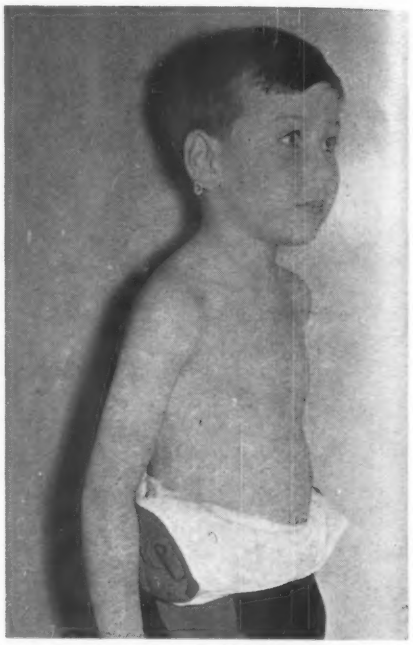

FIG. 10.—Case 1. At the age of 5 years. He has a slight chest deformity.

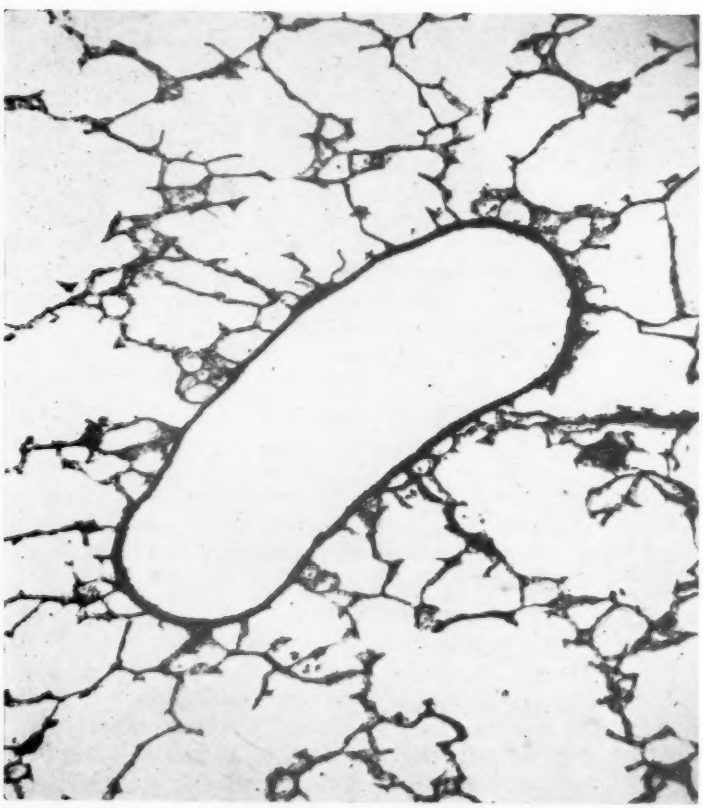

FIG. 9.—Case 3. Complete absence of cartilage in the wall of the medium-sized bronchus. ×50.

In all of these cases the affected lobe has been the left upper, but in the available literature the lesion has been noted also in the right upper lobe and the right middle lobe, but only once, by Caffey (1953), in the left lower lobe. The upper lobe bronchi are generally more liable to present anatomical variations.

Despite the somewhat varied clinical manifestations of this disease the radiological appearances in all these cases were similar. These are (1) emphysema of an upper lobe; (2) collapse of a lower lobe on the ipsilateral side; (3) considerable mediastinal shift away from the lesion and anterior mediastinal herniation.

Summary

Three cases of congenital lobar emphysema are reported. In the first of them the disease was discovered accidentally at the age of 4 months. As a 5-year-old he appeared in good health without having been submitted to operation. Case 2 had severe manifestations of anoxia leading to convulsions pre-

operatively and persistence of some degree of respiratory disability after lobectomy. Progress in the third case was uninterruptedly favourable since operation. The bronchial ramifications of the removed lobe were almost completely devoid of cartilage.

We wish to express our gratitude to Mr. Graham Bryce for permission to follow up Case 1; to Mr. Dewsbury and Mr. Dark for their cooperation and reports on the findings at operation in Cases 2 and 3; to Dr. Duran-Jorda for the histological investigation and to the Department of Medical Illustration for the *x*-ray prints. We are also indebted to Professor Wilfrid Gaisford for his kind and helpful criticism.

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COR TRIATRIATUM: CONGENITAL STENOSIS OF THE COMMON PULMONARY VEIN

BY

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Cor triatriatum is the term given to a rare congenital abnormality of the heart in which a septum separates what is apparently one of the atria into upper posterior and lower anterior chambers. With few exceptions, the septum has always been present on the left side of the heart. Other names given to the same anomaly naturally reflect the authors' views concerning the nature and origin of the extra chamber. Thus Loeffler (1949) reported his case as a 'heart with pulmonary sinus' and Edwards, Du Shane, Alcott and Burchell (1951) have referred to 'stenosis of the common pulmonary vein'.

From the functional aspect, three varieties of the condition have been described (Loeffler, 1949). In one, there is no communication between the accessory chamber and the left atrium. Death is inevitable immediately after delivery unless there is some other anomaly allowing blood to escape from the accessory chamber as in Case 3 of Edwards *et al.* (1951). At the other extreme there is an opening in the septum which is relatively large so that there is little or no obstruction to the flow of blood through the left side of the heart as in the patients of Loeffler (1949) and of Griffith (1903). In the intermediate variety the communication between the accessory chamber and the left atrium consists of one or more small openings which offer considerable obstruction to blood flow.

The following is the report of a patient who comes into this last category.

Case Report

J.B., a male infant, aged 7 weeks, was admitted to hospital on July 15, 1954. Pregnancy had been uneventful and the infant was delivered at full term after a normal labour. The birth weight was 7 lb. 4 oz. Both parents and an older child aged 3 years were in good health. The child appeared normal at birth and thrived satisfactorily until the onset of the present illness. Five days before admission to hospital he developed an irritant cough and began to vomit his feeds. These symptoms became progressively worse and he was therefore referred to hospital. On admission, he was slightly cyanosed and had signs of consolidation at the right lung base: temperature 97° F.; pulse 150/minute, regular; respirations 60/minute. The heart was not clinically enlarged and no murmur could be heard. The other systems were normal. The infant was nursed in oxygen and given penicillin parenterally and sulphadimidine by mouth. Initially there was some improvement but a few days after admission obvious signs of congestive heart failure developed; the liver enlarged rapidly and pitting oedema of the sacrum, buttocks and legs appeared. Treatment with 'digoxin' was begun but the congestive heart failure responded only temporarily and the patient died 13 days after admission.

Investigations during life showed that the urine contained a trace of albumin, but on microscopy was normal.

A radiograph of the chest (portable film) showed apparent enlargement of the heart. There was bronchopneumonic shadowing at the right lung base. The left lung was largely obscured by the heart shadow. Unfortunately, an electrocardiogram was not taken, and the child was considered too ill for heart screening.

Necropsy

The pathologist's report is as follows:

'The body shows no external abnormalities and is well nourished. The heart is enlarged and weighs 43 g. The enlargement is due to right ventricular hypertrophy. The right atrium is dilated and communicates normally with the superior vena cava and inferior vena cava. The foramen ovale is patent and the opening measures 5 mm. The left ventricle is small and there is no interventricular septal defect. The left atrium is divided by a septum into two chambers, postero-superior and antero-inferior. These communicate by a small opening in the septum, approximately 1 mm. in diameter, which is situated just above the posterior cusp of the mitral valve. The upper chamber or supernumerary atrium receives three pulmonary veins, two on the right side and one on the left. The lower chamber has the foramen ovale in its medial wall and communicates with the left ventricle through a normal mitral orifice. The left auricle forms part of the lower chamber. A drawing of the specimen is reproduced in Fig. 1.

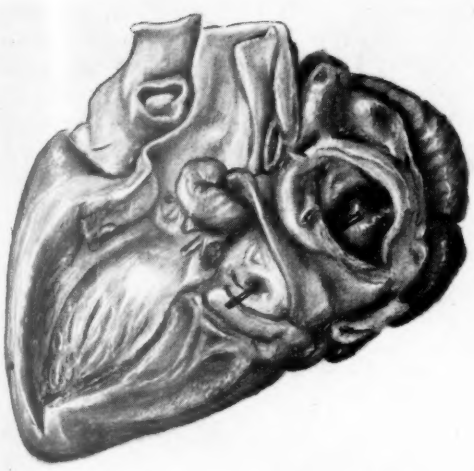

FIG. 1—A drawing of the left antero-lateral aspect of the heart showing a probe passing through a small opening in the septum which separates the upper and lower chambers. The latter communicates with a small left ventricle through a normal mitral orifice.

'The other organs appear anatomically normal and show the changes of chronic venous congestion.

'Microscopic examination of the heart shows that the muscle is normal and there is no evidence of fibroelastosis. The septum dividing the left atrium into two chambers is composed of fibrous tissue and cardiac muscle, and the upper and lower surfaces are covered by endothelium. The lungs, liver and spleen show the features of chronic venous congestion.'

Discussion

The heart lesion discovered in our patient is undoubtedly very rare. Maud Abbott (1936), in an analysis of 1,000 necropsies of congenital heart disease, mentions 14 cases in which atrial septa were present and were considered to be the primary lesion responsible for death. In 10, the septum was in the left atrium (age range, birth-48 years; mean, 20 years; four males and six females).

Pedersen and Therkelsen (1954) have reviewed the reports of 19 cases of left-sided cor triatriatum in the world literature and added one of their own. They also found references to three other cases in which clinical and pathological data were lacking. Subsequent to their publication, there have been reports of two other cases (Haarscher, Marcoux and Levy, 1954; Hartmann, 1955).

The following short summary includes the relevant points concerning our own patient, and therefore relates to 23 cases in all. The data contained in Abbott's (1936) publication have been excluded, since the sources of her cases are not given, and some of them are almost certainly included in Pedersen and Therkelsen's review.

Age. Most of the patients have died in infancy or in the first few years of life. Thus, of the 23 examples of the condition, 17 patients died before the age of 12 years, and of these nine died within the first six months of life. The age at death is not recorded in one patient. In all the childhood deaths, the opening in the septum was less than 6 mm. in diameter. Those patients who reached adult life had relatively large septal openings (Church, 1868; Fowler, 1881-82; Preisz, 1889), with the exception of Pedersen and Therkelsen's patient (see below), a woman who lived until the age of 29 years and in whom the orifice in the septum was estimated at 5-7 mm. in diameter.

Sex. The sex incidence is equal; of 21 cases in which the sex is recorded, 10 were males and 11 females.

Clinical Features. In some of the patients progress had been normal until shortly before death, as in the present child, and the terminal feature had been a rapidly developing congestive heart failure. In others, as in many examples of congenital heart disease, recurrent respiratory infections had been encountered. Often there is no definite cardiac enlargement on clinical examination and in several patients no heart murmurs have been heard. Tachycardia is a common feature and this may well obscure any murmur that might be present at slower rates. Other signs include those of bronchopneumonia and of right-sided heart failure. Electrocardiograms were recorded in five patients only, and in all right axis deviation was present together with signs of right ventricular hypertrophy. The patient described by Pedersen and Therkelsen (1954) seems to be the only one in whom detailed cardiovascular studies were made before death. These authors recorded the details of a 29-year-old woman suffering from increasing cardiac distress and in whom radiological, electrocardiographic and catheterization studies pointed to pulmonary hypertension due to obstruction in the venous side of the lesser circuit. Thoracotomy was undertaken in order to relieve what was presumed to be mitral stenosis, but a normal mitral valve was encountered. At necropsy the typical findings of cor triatriatum were discovered.

Angiocardiography has not yet been employed in any of these patients.

Morbid Anatomy. The usual picture is that of a diaphragm which separates the left atrium into an upper posterior chamber receiving the pulmonary veins, and a lower anterior one which contains the

mitral orifice. The auricle always opens into the lower chamber. The septum is never more than a few millimetres in thickness and may be extremely thin. The perforation in the septum is usually single but there may be several. In two cases (Stöber, 1908; Tannenburg, 1930) the diaphragm was intact and the only exit of blood from the chamber was through an atrial septal defect in both, and also, in the first case, through anomalous pulmonary veins.

Other congenital defects are not frequent; they are usually in the nature of atrial septal defects which may communicate with either the upper or lower chambers of the left atrium.

Naked-eye and histological findings of endocardial fibro-elastosis have been noted in a few patients (Doxiadis and Emery, 1953).

The Nature of the Malformation. Several hypotheses have been put forward to explain the malformation in terms of embryology. These have been critically reviewed by Loeffler (1949) and Parsons (1950). The modern concept was anticipated many years ago by Griffith (1903) who suggested that there was 'a failure in the complete amalgamation of that part of the auricle which is said to be formed from the confluent portions of the pulmonary veins and that derived from the left hand division of the common auricle of the embryonic heart'. This has been put in a more concise way by Edwards *et al.* (1951), according to whom the malformation is a result of developmental arrest at the stage when the sino-atrial region of the heart develops the evagination which later becomes the common pulmonary vein, a process which has been demonstrated in the human embryo (2 to 7 mm.) by Auër (1948). The accessory chamber, which receives the pulmonary veins, exists because of failure of the normal incorporation of the common pulmonary vein into the left atrium. It is thus a dilated common pulmonary vein, and the septal opening represents the junction of the sino-atrial portion of the heart with the embryonic common pulmonary vein. The septum is therefore formed by the posterior wall of the primitive left atrium and the inferior wall of the dilated common pulmonary vein.

Diagnosis. As yet no patient with cor triatriatum has been diagnosed in life; but it is not improbable that eventually this will be accomplished. The importance of doing so lies in the fact that this condition, if unaccompanied by other congenital heart anomalies, is, on theoretical grounds, suitable for surgical treatment. Without detailed investigation the diagnosis at best can be suspected in any patient with pulmonary hypertension of obscure origin and with electrocardiographic signs of right ventricular hypertrophy.

Probably the only certain way to establish the diagnosis in life would be to carry out an exploratory thoracotomy. Before cardiotomy, the demonstration of a high pressure in the pulmonary veins with a normal pressure in the left atrium would give the surgeon some indication of what to expect. As pointed out by Pedersen and Therkelsen, the surgical approach in opening the heart may be of importance. Entrance through the auricular appendage (auricle) would be distal to the membrane and, as in their patient, a normal mitral valve would be encountered. This may lead to a mistaken diagnosis. Where the diagnosis is suspected it is suggested that entrance through a pulmonary vein would be preferable.

Summary

The details are recorded of a male infant who died in congestive heart failure at the age of 9 weeks. Post-mortem examination showed that the heart was affected by an extremely rare anomaly, cor triatriatum, or congenital stenosis of the common pulmonary vein. Reference is made to previously reported examples of the condition and a short analysis of age and sex distribution, clinical features and morbid anatomy is based on a total of 23 cases in the literature. The nature of the developmental defect and the possibility of operative treatment are briefly discussed.

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INFERIOR VENA CAVAL AND HEPATIC VEIN THROMBOSIS: THE CHIARI SYNDROME IN CHILDHOOD

BY

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The syndrome of hepatic vein thrombosis was first described by George Budd of King's College Hospital, London, in 1845. Chiari in 1899 reported three cases of his own and reviewed the literature. The first case in childhood (an infant of 17 months) was published by Gee in 1871, and since that time we have only been able to trace nine other examples of this syndrome under the age of 17 years in the world literature (Schüppel, 1880; Lazarus-Barlow, 1899; Fisher, 1902; Penkert, 1902; Fabris, 1905; Hess, 1905; Hutchison and Simpson, 1930; Thompson, 1947; Dodd, Johannsman and Rapoport, 1948; Bronte-Stewart and Goetz, 1952).

We have recently investigated a boy aged 13 years with hepatic vein thrombosis. An associated panniculitis, together with other clinical and pathological findings which throw some light on the aetiology of the thrombosis, prompted this report.

Case Report

D.C., a boy aged 10 years, had been an in-patient from September, 1952, to February, 1953, at a general hospital elsewhere, suffering from fever, debility, joint pains and tender nodules on the legs. His infancy, childhood and development before this illness had been normal and the family history was not remarkable.

No abnormality was detected clinically apart from recurrent 'erythema nodosum' on the legs. The temperature varied between 97 and 101° F. and the E.S.R. between 17 and 27 mm. in one hour. The white blood cell count ranged from 7,000 to 12,000 per c.mm. with a normal differential count, and the haemoglobin remained steadily at about 75% (Haldane). Frequent examinations of the urine showed no abnormalities. The Mantoux test was negative. A radiograph of the chest was normal.

During 1953 he attended school and remained fairly well with only occasional crops of erythema nodosum. In May, 1954, he was readmitted to the same hospital because of an exacerbation of the eruption and fever, a diagnosis of chronic meningococcal septicaemia being then entertained. Repeated blood cultures (aerobic and anaerobic) were, however, sterile. Cerebrospinal fluid, radiographs of the chest and agglutination tests were not informative, but the serum globulin was raised (3·97 g. per 100 ml.). A muscle biopsy was negative.

In March, 1955, he was admitted to the Royal Manchester Children's Hospital because of malaise, anorexia and recent loss of weight. He still had pains in the joints and tender patches on the legs, and there was occasional abdominal pain on walking. He was an intelligent, delicate-looking boy, 64 in. in height and 79 lb. in weight. Clinical examination was essentially negative apart from the eruption on the shins, thighs, calves and, to a lesser extent forearms. This consisted of rosy papules about 1 cm. in diameter, slightly itchy on first appearing, becoming duskier over the course of 24 hours and fading over the next few days, leaving a faint purple staining with some deep induration but no superficial scarring or atrophy of the skin. The abdomen was soft and a little full, with no tenderness, free fluid or organic enlargement. The E.S.R. was 10 mm. in the first hour and the Mantoux test strongly positive in a dilution of 1/100 (10 T.U.). The blood picture was normal.

On April 23, 1955, he complained of slight epigastric discomfort and was noted to have suddenly developed marked distension of the abdomen. There was complete anorexia but no vomiting, jaundice or constitutional upset. Tense ascites was evident, with a prominent venous network peripherally placed round the upper abdomen, particularly on the right side. The liver was enlarged four fingerbreadths, very firm but not tender. There was no splenomegaly and no oedema of the lower limbs although the pulses below the popliteals were now not palpable. Paracentesis abdominis yielded 6 pints of sterile, yellow cloudy fluid, containing 4% protein but few cells.

The suddenness of these developments, the massive ascites, hepatomegaly and absence of oedema or splenic enlargement, suggested thrombotic occlusion of the hepatic vein.

Other investigations yielded the following results: Blood urea 21 mg. per 100 ml., serum calcium 4·5 mEq./l., serum sodium 133 mEq./l., serum potassium 4·9 m.Eq./l., serum bilirubin 0·5 mg. per 100 ml. and serum alkaline phosphatase 5 (King-Armstrong) units. The thymol turbidity was 2 units (flocculation 0). The serum protein level was 6·4 g. per 100 ml. (albumin 2·8 g., globulin 3·6 g.) and serum cholesterol 75 mg. per 100 ml. (free

cholesterol 28 mg.). The urine was negative apart from large amounts of urobilin. Tests for occult blood in the stools were negative.

Radiograph of the chest, skeletal system, alimentary and urinary tract contributed nothing and an E.C.G. was normal. The Wassermann, Sabin-Feldman dye test, Paul Bunnell and other agglutination tests were all negative.

During the next few weeks he required twice-weekly paracentesis to control the ascites, and gradually developed pitting oedema of the lower extremities, abdominal wall and lower chest with increased prominence and extension of the venous network. Biopsy of a skin nodule showed a localized dense infiltration of polymorphonuclear cells confined to the fatty tissues with no overlying reaction.

On May 22, having been almost symptom-free up to this time, the patient developed sudden, severe substernal pain, dyspnoea and cyanosis. During the day there was rapid deterioration with increasing cervical venous engorgement and shortly before death a profuse petechial eruption over the chest and neck.

Necropsy

The liver was greatly enlarged and red-black with yellow areas of necrosis. Thrombi could be seen in the medium-sized branches of the hepatic veins. The inferior vena cava from just below the right auricle, up to and including the mouths of the hepatic veins, showed great thickening of the wall and narrowing of the lumen with almost complete obliteration by organized thrombus. White laminated clot with a little more recent thrombus was found to cover the mouths and extend into the channels of the hepatic veins (see figure). There were no unusual features in the portal vein, but the spleen was somewhat enlarged. Collateral circulation in the ligaments of the liver was not prominent, but the vena azygos was greatly dilated measuring rather more than a centimetre in diameter.

The entry of the inferior vena cava into the right auricle was obstructed by a thin grey membrane with tiny fenestrations in some areas. The attachment of the membrane to the circumference of the cardiac orifice was complete. Microscopic examination showed thin endothelial coverings with a central layer of cardiac muscle. There was no evidence of infiltration, whereas the walls of the veins covered by thrombus were infiltrated by polymorphonuclear and plasma cells with occasional eosinophils. Small vegetations were present in the right auricle just above the inferior vena caval opening and these were seen to be inflammatory in type with underlying cellular reaction.

Inflammation of fatty tissues was confined to the subcutaneous regions with no involvement of visceral fat. There were, however, numerous haemorrhages in the latter, in addition to many of the visceral and connective tissues. The arch and upper portion of the descending thoracic aorta were encased in blood, microscopic examination showing haemorrhage confined to the adventitia and outer layers of the media.

The capsules of the kidneys were rather adherent and there were scattered, small cortical scars. These were found to be wedge-shaped areas of fibrosis with infiltration by chronic inflammatory cells and similar areas of destruction were noted throughout the cortex, together with occasional glomerular scars.

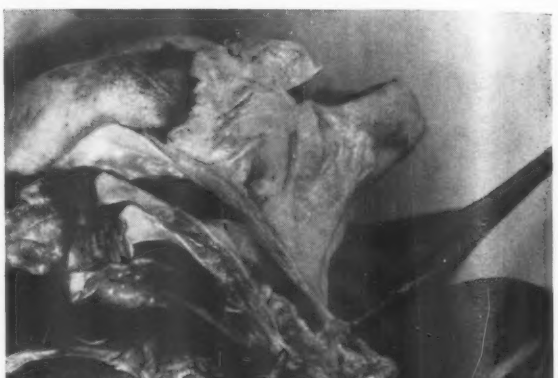

FIGURE.—The right auricle and inferior vena cava showing great thickening of the wall of the latter with thrombus in the lumen. The obstructing membrane described in the text can be seen between the tops of the forceps and a vegetation is present on the auricular wall just above this point. Note the areas of engorgement and necrosis on the cut surface of the liver.

Bacteriology

A staphylococcus was isolated from the right auricular vegetation and also from the thrombus in the inferior vena cava, the blood culture being sterile. As the organisms were coagulase negative and gave no reaction to typing phages, it is difficult to interpret the significance of these findings. In addition, sections stained by Gram's method failed to show the presence of organisms.

Discussion

Chiari Syndrome. When the many causes of secondary thrombosis of the hepatic vein are excluded, for example, tumours, lymphadenitis and blood diseases (Hirsh and Manchester, 1946) in which the thrombosis is merely a fortuitous phenomenon, there remains a group of cases in which the aetiology is obscure. Veno-occlusive

disease of the liver (Jelliffe, Bras and Stuart, 1954) appears to be a distinct clinical and pathological entity in which the large hepatic veins are not involved.

The importance of congenital anomalies in the hepatic vein and inferior vena cava has been suggested. Nishikawa (1918) stated that rudimentary valves in the inferior vena cava might be concerned in the causation of the thrombosis. Bennett (1950) described a case of obstruction of the inferior vena cava by a fibrous membrane at the level of the diaphragm. The patient was 60 years of age, but the lesion was regarded as being congenital in origin. The fenestrated membrane in the present case had a central core of cardiac muscle and the covering endothelium was intact. There was no evidence of inflammation and the situation coincides with that of the Eustachian valve, a remnant of its important foetal analogue.

Hepatic vein thrombosis was suggested by the sudden enlargement of the liver, associated with the development of ascites and engorged veins over the lower chest and abdomen. This conforms with the well recognized clinical picture which has been adequately reviewed by Thompson (1947). The collateral venous channels were situated centrifugally and did not converge upon the umbilicus to form a caput medusae as is seen in portal vein thrombosis. Another differentiating feature was the absence of conspicuous splenomegaly.

The striking clinical picture contrasts with the relatively normal biochemical findings with the notable exception of the lowered serum cholesterol level. Jaundice is absent. The widespread haemorrhages in our case were attributed to terminal liver failure.

The Chronic Illness. The nature of the protracted illness characterized as it was by vague ill health, with intermittent fever, joint pains and the eruption of nodules on the lower limbs over two and a half years, posed a problem in diagnosis. Rheumatism or a disease of the collagen group, tuberculosis, brucellosis and other chronic infections were considered, but there was no adequate evidence of these conditions, either clinically or at necropsy. The hyperglobulinaemia was consistent with sarcoidosis, chronic infection or a disease of the collagen group. The absence of a murmur and frequent negative blood cultures seemed to exclude infective endocarditis. However, necropsy showed evidence of a chronic blood-borne infection in the scarred, but otherwise normal kidneys and right auricular vegetations, which were thrombotic and not degenerative in type (Allen and Sirota, 1944).

It seems, therefore, that a congenital ' valve ' in the inferior vena cava, though impeding to some extent the venous return, caused no significant venous obstruction owing to the adequate collateral circulation. However, the stagnation of blood in what was virtually a cul-de-sac at the upper end of the inferior vena cava led to the development of infective thrombophlebitis and subsequently endocarditis. This marks the onset of the fluctuating pyrexial illness. Scarring in the affected vessel with caudad deposition of laminated clot continued until the mouths of the hepatic veins were occluded, producing the arresting picture described.

It seems evident from our case that a focus of infection situated in a large vein must be considered in patients with chronic bacteraemia. Furthermore the repeated negative blood cultures emphasize the difficulty of excluding such a diagnosis by this method.

The Panniculitis. The rash showed certain distinct differences from erythema nodosum. The more widespread distribution, the small size, relative painlessness, rapidity of maturation and disappearance together with the incipient necrosis and subcutaneous infiltration which was entirely neutrophil in type, all militated against this diagnosis. The picture conforms rather with the relapsing panniculitis described by Rothmann and Makai (cited by Carleton, 1949), and elaborated by Baumgartner and Riva (1945). While there is no uniformity of opinion as to the causation of this disease, it usually occurs as a sequel to infection, for example tonsillitis, phlebitis or bronchiectasis (Carleton, 1949). In a case of pannicultis described by Miller and Kritzler (1943) dental extraction was followed on two occasions by a crop of nodules. In another (Baumgartner and Riva, 1945) an attack of tonsillitis preceded a similar eruption on no less than three occasions. The blood cultures in all cases, however, have been repeatedly sterile. Impaired circulation has been considered a factor, but although this was certainly present in the lower extremities in our case, occasional nodules were found on the upper limbs.

Summary

A case of thrombosis of the inferior vena cava and hepatic veins diagnosed during life is presented and the aetiology of this condition is discussed.

The incidence of the Chiari syndrome in childhood is briefly reviewed.

The causation of an associated recurrent panniculitis is examined.

We are indebted to Professor W. F. Gaisford for invaluable criticism, and to Dr. T. N. Fisher for permission to publish this case. Our thanks are also due to Mr. A. E. Ward for the photograph.

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HYPERVITAMINOSIS A

BY

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Since Josephs (1944) first described hypervitaminosis A there have been numerous cases reported in the American literature, notably by Toomey and Morissette (1947) and by Caffey (1950 and 1951). No record of such cases has been traced in the British literature and so the occurrence of two examples of this condition is thought to be worthy of record.

Case Reports

Case 1. R.P., a boy of 6 years, was admitted to the Wakefield General Hospital on March 9, 1955. He had had frequency of micturition and nocturnal enuresis for two weeks. This was followed by vomiting and anorexia for one week. Then he developed pain in the arms, legs and forehead of such severity as to prevent him from sleeping. He was thought to have lost weight during the previous three weeks.

Xeroderma had been diagnosed at the age of 5 months and had been treated by ointment until a dermatologist prescribed 'avoleum', a dram b.d. This was continued until six weeks before admission when the dose was increased, probably by the mother, to 'avoleum', drams 2 b.d. It was estimated that the intake of vitamin A over the six weeks before admission was about 463,040 i.u. per day.

On admission the child was ill and fretful with a temperature of 100° F. The skin was salmon pink and scaling. The lips and nasal mucocutaneous junctions were cracked and bleeding, and very sore. The arms and legs were extremely tender to the lightest touch, subcutaneous tissues were swollen, most markedly over the tibiae. The liver and spleen were both enlarged three fingerbreadths below the costal margin. There was a bilateral conjunctivitis.

During the first week in hospital the skin became more scaly and the patient continued to complain of pain in the upper limbs and back which caused difficulty in sitting. Oedema of the face developed on March 13. The temperature dropped to normal by the end of the week.

A radiograph of the chest was normal (March 9).

On March 10 the haemoglobin was 93%, and the total white blood cell count 10,600 per c.mm. (neutrophils 60%, lymphocytes 38%, monocytes 2%). The E.S.R. was 17 mm. in one hour. The Mantoux test (1 : 1,000) was negative.

On March 11 the blood cholesterol level was 316 mg. per 100 ml.

On March 12 albumin + was found in the urine, and also occasional hyaline and granular casts and very occasional pus cells.

On March 15 the cerebrospinal fluid was normal. The blood urea level was 88 mg. per 100 ml.

During the second week the pain in the limbs and back subsided, and by the end of the week a considerable improvement in the skin was noticed, it being quite soft and moist. The dry, cracked lips persisted. On March 18 the prepuce swelled. The spleen was slightly smaller.

A radiograph of the skull and limb bones on March 17 showed normal appearances.

The serum bilirubin level was 0·3 mg. per 100 ml.

A trace of albumin and a few pus cells were found in the urine.

On March 21 a water dilution and concentration test was normal.

Thymol turbidity was 3 units.

The alkaline phosphatase level was 25·2 units per 100 ml.

The blood carotene was 20 μg. per 100 ml. and the blood vitamin A, 450 i.u. per 100 ml. (normal 50-130 i.u. per 100 ml.).

The oedema of the prepuce had cleared by the third week, and, apart from cracked lips (Fig. 1), the boy was

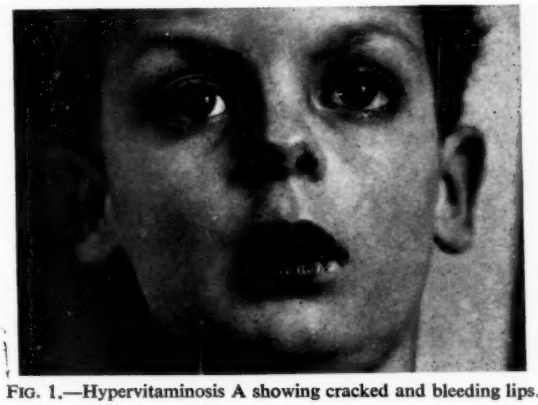

FIG. 1.—Hypervitaminosis A showing cracked and bleeding lips.

free of symptoms. The liver had reduced slightly in size, and the urine was normal. On March 26 the blood urea level was 40 mg. per 100 ml.

At the end of the fifth week the hair was being shed

and the scalp became scaly. The rest of the skin was in good condition.

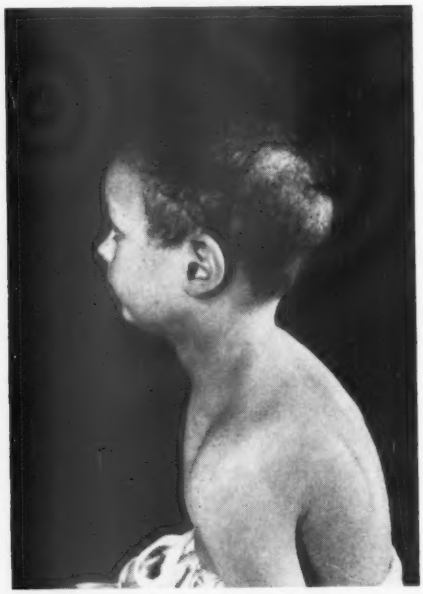

FIG. 2.—Hypervitaminosis A showing loss of hair.

On April 4 the blood urea level was 21 mg. per 100 ml., and the urine normal.

On April 6 alkaline phosphatase was 32 units per 100 ml., serum calcium 10·5 mg. per 100 ml. and blood cholesterol 187 mg. per 100 ml.

By the end of April the boy's hair was shed in handfuls (Fig. 2). The skin was becoming dry and ichthyotic. The spleen and liver, although reduced in size, were still palpable.

A radiograph of the clavicle on April 25 was normal. The left humerus showed an area of osteoporosis in the upper third of the shaft.

On April 26 the blood carotene level was 20 μg. per 100 ml., and the blood vitamin A 150 i.u. per 100 ml.

On April 27 the blood urea level was 22 mg. per 100 ml., haemoglobin 86%, E.S.R. 12 mm. in one hour. The total and differential white blood counts were normal.

On April 28 the alkaline phosphatase level was 37 units per 100 ml.

On May 23 the blood carotene level was 30 mg. per 100 ml., and the blood vitamin A 90 i.u. per 100 ml.

On May 27 the thymol turbidity was 1 unit per 100 ml. and alkaline phosphatase 26·9 units per 100 ml.

On August 9 the child was well but the liver and spleen were still just palpable. The skin was ichthyotic but the hair was growing well.

Case 2. S.W., a girl aged 4 years, was admitted to the Clayton Hospital, Wakefield, on April 12, 1955. The complaint was of anorexia and malaise, pains in the forehead, wrists, forearms and shins, and facial and temporal swelling for two weeks. There was a loss of weight during the same period. There had been severe epistaxis and also pain and discharge from the ear during the previous two days.

The child had no previous illness apart from ichthyosis for which she had been given 'avoleum', 1 dram t.d.s. (347,280 i.u. per day), from a dermatological department for the past two years.

On admission the child had a temperature of 101° F. She had a scaling, patchy erythematous rash on the upper parts of the arms and trunk. The lips were crusted and bleeding. There was oedema of the eyelids, and the temporal regions were so swollen that the face had a triangular appearance. The shins and forearms were tender to the lightest touch.

The liver was enlarged two fingerbreadths below the costal margin. The spleen was impalpable.

There was a bilateral otitis externa with an underlying otitis media on the right side. The throat was injected.

During the first week in hospital the general condition slowly improved and the temperature was normal in five days. The facial and temporal swelling subsided in three days, but the eruption became more extensive, covering the forearms and abdomen with erythematous patches (Figs. 3 and 4). The skin became dry and scaling and the lips cracked. The tenderness over the long bones became gradually less and at the end of the week there was only slight tenderness over the tibia.

Treatment with penicillin cleared the ear infection. The size of the liver became slightly less.

FIG. 3.—Hypervitaminosis A showing macular rash in the acute stage.

On April 13 haemoglobin was 78% (11·6 g.), W.B.C.s 12,800 c.mm. (polymorphs 85%, lymphocytes 13%, monocytes 2%). The B.S.R. was 17 mm. micro in one hour.

The urine showed albumin + and reduced Benedict's

solution. A chromatogram showed glucose. There were a few pus cells and casts.

A swab from the ears on April 14 yielded a heavy growth of penicillin-sensitive *Staphylococcus aureus*.

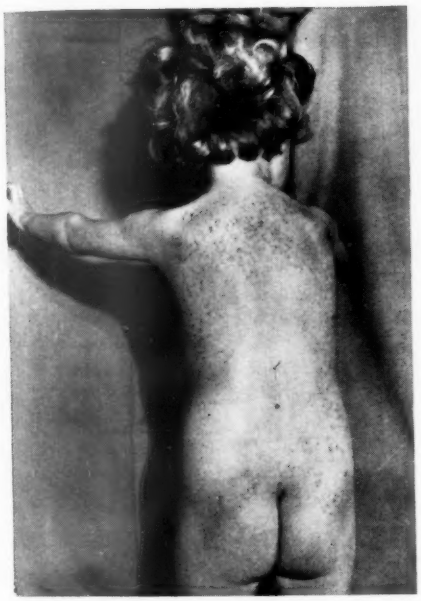

FIG. 4.—Hypervitaminosis A showing macular rash in the acute stage.

Radiographs showed that both mastoid regions appeared normal and a little generalized congestion in the chest.

Radiographs of the wrist and arms on April 15 showed increased density at the growing ends of the shafts of the long bones but no actual irregularity, and no abnormality of the spine and clavicles.

On April 19 the blood carotene level was 20 μg. per 100 ml. and blood vitamin A 700 i.u. per 100 ml.

By the end of two weeks the child was in good general health. The rash and facial swelling had gone but the skin was dry. At the beginning of the third week the hair became dry and lifeless and could easily be pulled out, and soon was shed in handfuls, only a sparse growth remaining. The liver was only just palpable.

On April 26 the blood urea level was 34 mg. per 100 ml. A three-day vitamin C saturation test when 125 mg. ascorbic acid was given each day, gave daily excretions of 2·1, 2·1 and 8·9 mg. (normal for weight 12·5 mg.).

On April 28 the alkaline phosphatase was 41 units per 100 ml., serum phosphorus 3·9 mg. per 100 ml., serum calcium 10·8 mg. per 100 ml. and serum cholesterol 140 mg. per 100 ml.

By July 12, 1955, the hair was growing. The liver and spleen were not palpable. The skin was normal.

On review on November 11 the ichthyosis was returning; the hair was normal and the child well.

Discussion

It has long been known that polar bear's liver produces acute vitamin A poisoning. Rodahl and Moore (1943) found that the vitamin A content of the liver was equivalent to 8,000,000 i.u. in 0·5 kg. The symptoms produced are headache, hyperirritability followed by drowsiness, desquamation of the skin at the mucocutaneous junctions in 24 hours, with peeling of the entire skin in a few days.

Chronic poisoning due to vitamin A has been well described by Caffey (1950 and 1951) following on the earlier descriptions by Toomey and Morissette (1947) and Josephs (1944).

In nearly all the cases described previously the poisoning was due to excessive and prolonged administration of either halibut liver oil or oleum percomorphum. I have not been able to trace any previous record of a case due to a pure vitamin A product such as 'avoleum'.

From the previous accounts a fairly uniform clinical picture can be drawn. The initial symptoms are usually anorexia, fretfulness and itching of the skin. Tender subcutaneous swellings appear over the long bones and skull. Fissures appear on the lips and other mucocutaneous junctions with cracking and bleeding of the mucosa. Cortical thickening of the long bones is usual after the vitamin has been given for six to 15 months. In neither of the above cases was this found, although in Case 2 it was thought that early changes in the long bones could be seen, but the appearances were not very convincing.

The absence of changes in the bones in Case 1 might be due to the fact that a very high dosage was given for only six weeks before symptoms appeared.

Caffey (1950) notes that there is a latent period of several months between the start of the excessive dosage and the appearance of diagnostic clinical signs. The length of this period did not depend on the size of the overdose and the shortest latent period was six months. In his series the earliest radiological observation, showing cortical hyperostosis in the ulnas, was three weeks after the onset of symptoms. It may be that in the two cases described here that as this interval was less than that period the hyperostosis had not time to develop.

Loss of hair and dryness of the skin associated with an erythematous rash also characterize the condition. Both our patients had this typical scaly erythematous rash on the trunk in the early stages of the illness and both lost much of their hair (Fig. 2). After the vitamin A was stopped and the rash had cleared there was a period in which the skin was soft in texture and normal in every way, but this was ultimately followed by a relapse to the ichthyotic

state. This period in which the skin was normal was presumably sustained by the gradual release of vitamin A stored in the liver.

The liver and spleen are often found to be enlarged in hypervitaminosis A and in Case 1 both are still palpable 10 months after admission. This leads one to think that serious and permanent liver damage may be produced by prolonged administration of the vitamin, and makes one wonder whether the possible toxic effects should be lightheartedly dismissed as in some recent statements.

The most characteristic feature of the condition is that once the vitamin A is stopped the signs and symptoms regress and there is rapid recovery. The tenderness, pain, anorexia and irritability usually disappear within one week.

The most valuable investigation is the estimation of the vitamin A blood level showing a rise above the normal level of 50-130 i.u. per 100 ml.

The one condition with which vitamin A poisoning may be confused is infantile cortical hyperostosis. Caffey (1950) pointed out that the latter condition always appears in the first four months of life, whilst hypervitaminosis A is usually not seen before the end of the first year. He states that cortical thickening of the bones is seen in both conditions, the face and jaw are swollen and the mandible thickened in every case of infantile cortical hyperostosis, these structures being unaffected in vitamin A poisoning. The blood levels of vitamin A are normal in cases of infantile cortical hyperostosis.

In conclusion it should be emphasized that the dosage of 'avoleum' recommended by the manufacturers is unlikely to produce symptoms. It would appear that in the treatment of skin conditions by vitamin A care should be taken if it is required to use high dosage for very long periods.

I wish to thank the Editor of the *Proceedings of the Royal Society of Medicine* for permission to publish these cases which were previously reported at the Section of Paediatrics meeting on June 25, 1955 (*Proc. roy. Soc. Med.*, **48**, 1107).

I am grateful to Dr. W. L. Rose for the numerous biochemical and pathological investigations, and to Dr. G. A. Stevenson and Dr. A. M. Fraser for radiological reports. Dr. A. T. Haworth, of the Department of Chemical Pathology of the University of Leeds, kindly estimated carotene and vitamin A blood levels. Dr. J. M. Morfitt gave much valuable assistance in the preparation of the manuscript, and Mr. Wade, the Librarian of the Royal Society of Medicine, helped greatly in compiling the references. British Drug Houses Ltd. gave much valuable advice on the strength of 'avoleum' and the toxic effects of vitamin A.

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SUCCESSFUL TREATMENT OF A PERFORATED ROKITANSKY-CUSHING ULCER

BY

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From the General Hospital, Singapore

(RECEIVED FOR PUBLICATION FEBRUARY 27, 1956)

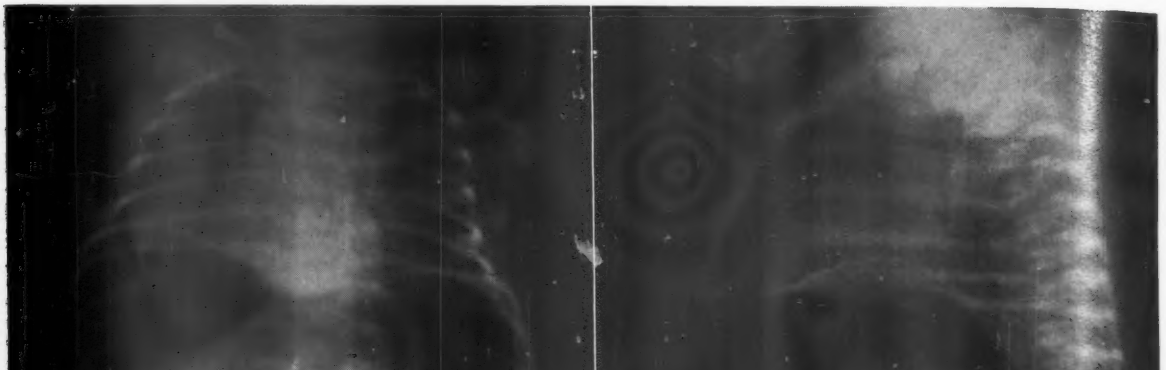
Peptic ulceration in infancy and childhood is now a well established clinical entity. The condition, its incidence and the pathological findings have been well described by writers such as Bird, Limper and Mayer (1941) and Guthrie (1942). Most early descriptions of the condition were usually an account of the necropsy findings. As a result of the greater publicity given to the condition, surgeons in general, and paediatricians in particular, began to look for the disease in life, and there is now a large volume of literature indicating the success with which this search has been rewarded. In the very lethal complication of perforation of the ulcer into the general peritoneal cavity, it has now been shown that successful operations can be performed even in very young babies. In these young babies, however, the problem has not been entirely solved and a mortality rate of about 90% (Rubell, Leix and Clelland, 1952) or 70% (Bird *et al.*, 1941) has been reported. There is, nevertheless, a slowly increasing number of successful operations being performed in these patients. Thus, Selinger (1932) described the successful closure of a perforated stomach ulcer in a 3-month-old baby.

Bird and his colleagues successfully closed a perforated duodenal ulcer in a 34½-hour-old baby. Léger, Ricard, Léonard and Piette (1950) were successful in a 6-day-old baby. To these may be added the case of Brink and Keyzer (1952) in a 1-day-old baby with a perforated duodenal ulcer and that of Schwartz and Halberstam (1943), in which the patient was 11 months old. In all these cases the disease had arisen as a single specific entity. They were examples of what Gross (1953) has called the primary peptic ulcer of childhood. The secondary peptic ulcers arise as complications of other diseases. These include the ulcers arising in association with burns (Curling, 1842), with sepsis, marasmus, general toxaemia or as a complication of intracranial disease. This last type of ulcer has been called the Rokitansky-Cushing ulcer. It would seem from the literature that this ulcer, especially when perforated, is a pathological finding at necropsy. Gross (1953) only mentions their occurrence. The rarity of this condition and the failure to find a record of a similar case have prompted this paper.

Case Report

The patient, a 10-month-old male Chinese baby, was admitted to the General Hospital, Singapore, on February 3, 1955. There was a history of two days' pyrexia associated with a slight cough. He had had convulsive attacks for one day. His temperature was 103° F. on admission. The anterior fontanelle was bulging. The child was having fits, mainly on the right side, although all limbs were involved. He was comatose. The head circumference was 19½ in. The pupils were dilated and did not react to light. Turbid fluid under pressure was removed from the spinal theca. No organisms were grown on culture. The child was treated with penicillin, sulphadiazine and luminal. The temperature was settling on February 7, when the baby vomited blood. Next morning the abdomen was distended, tense and tender. There was marked dyspnoea and the child was cyanosed. A radiograph of the chest was negative, but one of the abdomen (Fig. 1) showed a large collection of free gas under the diaphragm. A stomach washout was given, but there was no blood in the washings.

The child was put into an oxygen tent and a slow blood transfusion of 250 ml. given. The history, signs and radiological appearance were those of a perforated peptic ulcer with bleeding. In spite of the poor condition of the patient, it was decided that laparotomy was the only chance of cure. The anaesthetic, open ether with full and constant oxygenation, was administered by Dr. F. W. Pais. The abdomen was quickly opened through a right split rectus muscle incision. The peritoneum ballooned out before it was opened and air hissed out on opening it. There was a very little perforation on the superior border of the first part of the duodenum. It was about the size of a large pin-head and had a small amount of fibrin around it with a marked inflammatory reaction in the vicinity. The edges of the hole were quite soft. The perforation was well demonstrated by gently squeezing the second part of the duodenum when a small bead of bile could be seen issuing from the hole. The defect was closed by a fine catgut suture and the omentum tied



FIGS. 1 AND 2.—Radiographs showing gas under the diaphragm.

over this. A small drain was inserted and the abdomen closed. Post-operatively gastric suction was maintained for 24 hours and intravenous fluids given. There was very little drainage from the drainage tube. The convalescence was straightforward and eminently satisfactory. The sutures were removed on February 16. The child's cerebral condition slowly improved. He was listless for a time and had a right lateral rectus palsy. This had completely cleared when he was discharged on February 26.

Discussion

According to Cushing (1932), it was Rokitansky who was the first to draw attention to the association of the development of peptic ulceration in patients with brain and meningeal lesions. Cushing (1932) in his classical paper on the subject drew attention to the fact that in 11 cases of cerebral pathology there was at necropsy ulceration in the upper gastro-intestinal tract. It is for this reason that the type of ulcer described in the above case history is called a Rokitansky-Cushing ulcer in the same way that an ulcer following burns is known so well by the term Curling's ulcer. Ivy, Grossman and Bachrach (1951) state that it has been demonstrated beyond doubt that haemorrhagic erosions and acute ulcers of the stomach and duodenum occur in association with intracranial damage or disease. They point out, however, that it has not been shown that these acute digestive tract lesions depend on disturbances in the diencephalon and much less in some particular area within that division of the brain. Schlumberger (1951) found 10 such lesions incidentally in 251 consecutive necropsies. They were all acute, and were in the fundus and along the greater curvature of the stomach. He found that perforation was not common in this condition in children, and noted that when it did occur it was more common in gastric than in duodenal ulcers. They may be multiple. The theories postulated for the occurrence of these ulcers have been well described by Cushing and others and Schlumberger mentions that there may be a humoral factor such as the adrenocorticotrophic hormone involved in their production. Cook, Hartmann, Sarnoff and Beren-

berg (1951) have shown that peptic ulceration can occur in association with acute bulbar poliomyelitis.

Perforated peptic ulceration in children as a solitary lesion is not at all uncommon. It occurs in infancy and even in the neonatal period, and there are many references to this fact in the literature. Most perforations in the early days of infancy are fatal. All writers stress the importance of early diagnosis and treatment. Pointers to the diagnosis are shock, vomiting, haematemesis and/or melaena. Cyanosis and tachycardia are early signs (Wright and Scott, 1950) until the fifth day of the illness when clinical peritonitis becomes evident. It appears evident, therefore, that when a child is suffering from some intracranial disease and exhibits the features described, the possibility of there being an acute peptic ulcer should be borne in mind and steps taken to confirm or allay one's suspicions. As Gellis (1952) writes, 'patients with bulbar paralysis, meningitis and encephalitis as well as brain tumours, should be watched carefully for ulcer complication. Prompt institution of therapy might, in such cases, prove life-saving'. This case report bears out this prophesy in no uncertain manner.

Cases of perforation in the newborn and young babies have been successfully treated by operation as I have shown. These patients stand operation well, provided it is early enough. In these days of antibiotics, prompt operation can save the life of a child even when suffering from such a serious disease as meningitis.

This baby had an undoubted meningitis, even though the causative organism was not isolated: the bulging fontanelle, the turbid cerebrospinal fluid, convulsions, etc., were unmistakable evidence. In the course of a cure for this condition, the baby had a haematemesis and then a perforation of an undoubted ulcer. This, therefore, is a case of a Rokitansky-Cushing ulcer, and as such should have been fatal. Conservative measures such as those advocated by Taylor (1946) would in my opinion have proved unavailing. The tenseness of the abdomen, and the child's great respiratory embarrassment made it imperative to relieve the tension caused by the intraperitoneal air. Further, at operation there was no attempt by surrounding structures to seal off the perforation, whilst the omentum, so very small in this 10-month-old baby, was far removed from the site of the leak. Again, the child's general condition was deteriorating in spite of intragastric suction and intravenous therapy, and laparotomy was considered to be the only means of trying to save his life. Bleeding and perforation are a definite indication for operation in adults and should be an indication for operation in children.

The anaesthetic used was sufficient to give adequate relaxation and at the same time to ensure complete oxygenation. The approach by means of a split rectus incision is one I have used in many Rammstedt operations and led straight to the perforation. The manner of closing the perforation is one I have used so many times in adults and I have never had cause to worry about the possibility of obstructing the duodenum. I had in mind Ladd's advice on this danger in children. I have never hesitated to insert a suture in a suspected duodenal tear while doing a Rammstedt operation. I felt that the closure had been complete and thought that there would have been great difficulty trying to suture the omentum over the gap in view of the site of the perforation. Schwartz and Halberstam (1943) sutured the ulcer in their successful case and in the follow-up noted only a slight four-hour residue. The ulcer should be closed in the most convenient manner which is certain to be efficient, quickest to perform, and will cause the least trauma to this most important anatomical area.

Summary

The successful closure of a perforated Rokitansky-Cushing ulcer in a 10-month-old baby is reported, and the problem discussed with references to the literature on the subject.

My thanks are due to Dr. Quah Quee Guan for referring this case to me, and to Professor D. E. C. Mekie for allowing me to see and treat this case, and to the Director of Medical Services, Singapore, for permission to publish this report.

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CONGENITAL ABSENCE OF THE ABDOMINAL MUSCLES WITH ASSOCIATED ABNORMALITIES OF THE GENITO-URINARY TRACT

BY

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From the Royal Hospital, Wolverhampton

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The syndrome of congenital absence of the abdominal muscles associated with other abnormalities, chiefly of the genito-urinary tract, has received little attention in this country. Housden in 1934 reviewed 33 cases reported up to that time and added a further case of his own. Hill's (1947) case does not appear to have been a true example of this condition as there was a large defect of the anterior abdominal wall covered only by peritoneum.

Of the four cases presented here, three are examples of the condition while the fourth patient has suffered from recurrent chest infections.

Case Reports

Case 1. M.K., a boy, is the third child of healthy parents. Both siblings are boys and both are healthy. He was referred to hospital in September, 1953, at the age of 2 years and 1 month because of enlargement of the abdomen, which had been present since birth. The birth history and development up to that time was normal. On examination he was found to have a prominent abdomen with marked transverse creases. The abdomen bulged laterally, particularly to the right and especially noticeably on straining. The oblique and transversalis muscles were absent. The recti were present but deficient and divaricated. The liver and spleen were both palpable. The testes were bilaterally undescended. The blood pressure was 110/60 mm. Hg. The urine was found to be infected with *Staphylococcus aureus*. An intravenous pyelogram showed dilatation and elongation of both ureters but both kidneys appeared normal. A retrograde cystogram showed a thin bladder of abnormal shape with marked trabeculation.

The urinary infection was cleared with 'gantrisin' and chloramphenicol. The child was fitted with an abdominal corset and his mother instructed to make him urinate at regular intervals.

He remained well but was re-admitted to hospital in November, 1955, for re-assessment of the urinary tract. At that time he was a happy, well-nourished boy. He was passing urine normally and there was no incontinence. Physical examination showed no change. His urine was sterile and his blood urea level 43 mg. %. An intravenous pyelogram showed dilatation of the ureters, more marked on the left side, but no evidence of hydronephrosis. A retrograde cystogram showed an obstruction of the bladder neck (Fig. 1).

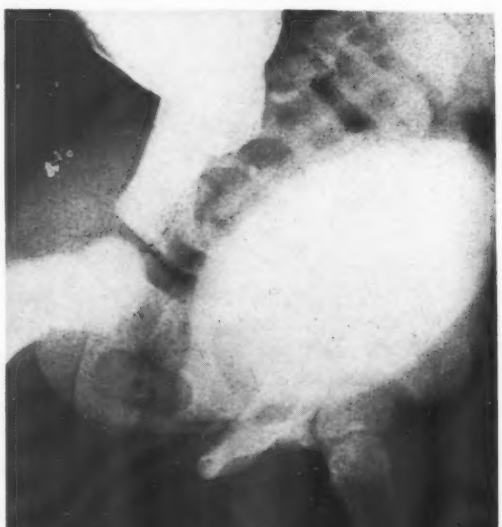

FIG. 1.—Retrograde cystogram in Case 1 showing a large bladder with dilatation of the posterior urethra.

Case 2. A.C. was admitted to hospital in March, 1952, at the age of 6 weeks. He was delivered by forceps following a full-time pregnancy. Birth weight was 8½ lb. Examination showed marked transverse creasing of the skin of the abdomen (Fig. 2). The oblique and transversalis muscles were absent. The left rectus was better felt than the right and it was noticed that in the supine position the abdomen tended to sag to the right. The abdominal organs were all easily palpable and the bladder was distended half-way up to the umbilicus. Blood pressure was 85/? mm. Hg. The urine was sterile. The blood urea level was 29 mg. %. A subcutaneous pyelogram was unsuccessful. A retrograde cystogram showed an enlarged bladder but no reflux to the

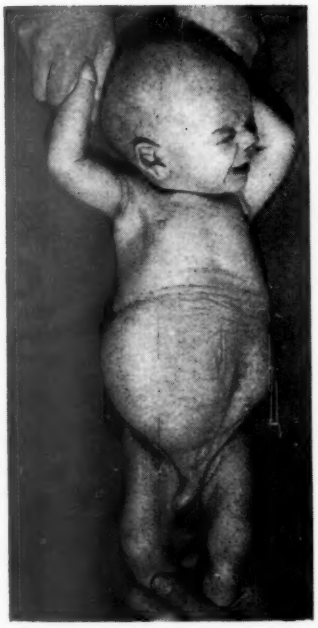

FIG. 2.—Case 2 showing typical appearance of the abdominal wall with transverse creasing and bulging flanks.

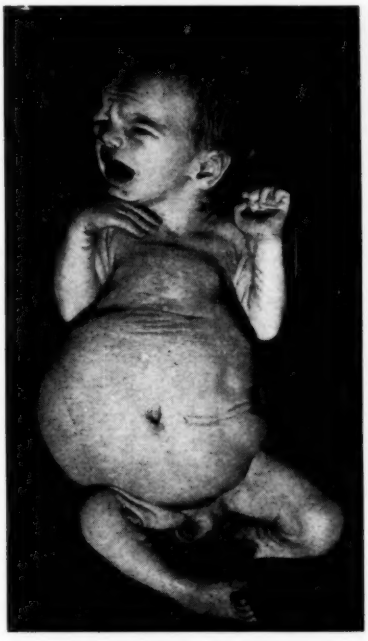

FIG. 3.—Case 3 showing appearance of the abdominal wall and the outline of the dilated left ureter.

ureters. The baby was fitted with an abdominal binder and discharged home.

He remained well but was re-admitted in May, 1955. The abdominal wall was bulging grossly. The bladder was palpable just above the symphysis pubis. Both testes were bilaterally undescended. Blood pressure was 90/55 mm. Hg. The blood urea level was 16 mg. %. A subcutaneous pyelogram showed bilateral gross hydroureter and hydronephrosis. A micturating cystogram was attempted but the patient refused to cooperate. He was again discharged home wearing his corset.

Case 3. K.M. was the second child of healthy parents, born following a normal pregnancy and weighing 8 lb. 4 oz. Delivery was difficult owing to abdominal enlargement and for this reason the infant was referred to hospital. The infant had not passed urine or meconium before admission.

On admission to hospital, six hours after birth, the abdomen was grossly enlarged. The anterior abdominal wall was thin and wrinkled and in both flanks there were visible distended, lobulated masses (Fig. 3), which resembled intestine but were considered to be enormously dilated and hypertrophied ureters. The bladder was palpable just below the umbilicus. The liver, spleen and kidneys were all palpable. The penis was abnormal in that the foreskin was excessively long with a small external opening. A small quantity of urine was present within the foreskin. Both testes were undescended. There was also a minor degree of talipes equino-varus, but no other abnormalities were found.

A diagnosis of absence of the anterior abdominal muscles was made, and an attempt was made to relieve the urinary obstruction. A dorsal slit was made and following the passage of a sound a No. 3 Coude gum-elastic catheter was passed and stitched *in situ*. A catheter specimen of urine was found to have a specific gravity of 1,002 and to be free of albumin. The blood urea level was 68 mg. %.

A retrograde cystogram showed gross dilatation of the bladder and reflux of dye up a markedly dilated left ureter (Fig. 4). A subcutaneous pyelogram confirmed the presence of a left-sided hydronephrosis. The right side appeared normal apart from spreading of the calyceal pattern.

The catheter was removed on the fourth day and the bladder was then emptied by manual compression.

On the seventeenth day the baby became febrile and examination of the urine showed a heavy *Bact. coli* infection. His general condition at this time was poor. The blood urea level was 92 mg. %. His condition gradually deteriorated and he died aged 31 days. At necropsy the ureters and kidney pelves were grossly dilated and distended with infected purulent urine (Fig. 5). The urinary bladder appeared to be divided into an upper and a lower chamber separated by an opening which just admitted the tip of a little finger. The lower chamber was thought to be a dilated posterior urethra. No organic urethral obstruction was found.

Case 4. R.D. was first admitted to hospital in December, 1951, 24 hours after birth because of per-

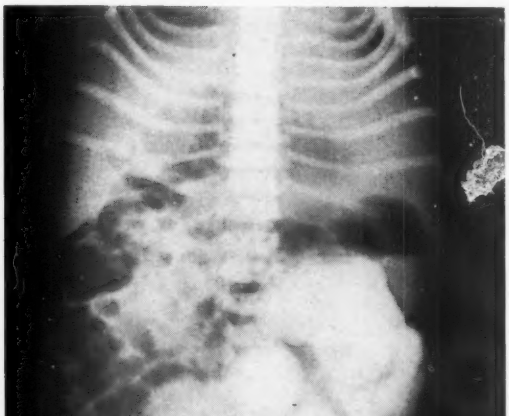

FIG. 4.—Retrograde cystogram in Case 3 to demonstrate reflux up the dilated and tortuous left ureter.

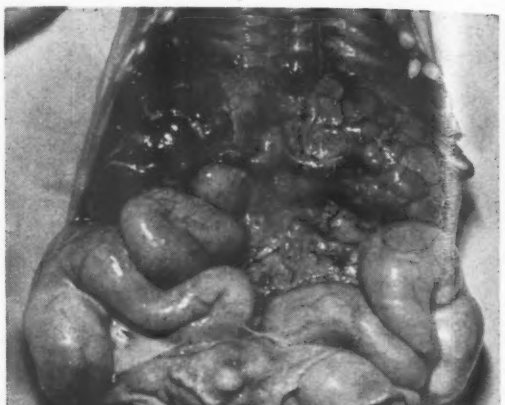

FIG. 5.—Appearance at necropsy in Case 3 showing the grossly hypertrophied and dilated ureters.

sistent cyanosis. He was the fourth child of healthy parents, the other children being free of abnormalities. His birth weight was 9½ lb. Examination showed a cyanosed infant, with a distended abdomen. The oblique and transversalis muscles were absent but the recti were present. Both testes were undescended.

He responded promptly to oxygen therapy and was discharged home.

Since then he had been re-admitted to hospital on at least 16 occasions because of recurrent respiratory infections. His latest chest radiographs in November, 1955, have suggested bilateral bronchiectasis. His present weight is only 34 lb.

Investigation has shown no abnormality of the urinary tract.

Discussion

The syndrome consists of either partial or complete absence of the anterior abdominal muscles associated with other congenital abnormalities. It occurs almost exclusively in males, although four cases have been recorded in females. The associated congenital abnormalities are chiefly of the genito-urinary tract, but numerous other anomalies have been noted. Amongst these are malrotation of the gut, talipes, cleft palate, spina bifida and hydrocephalus.

The commonest abnormal finding in the genito-urinary tract is hypertrophy and dilatation of the bladder together with bilateral hydroureters and hydronephrosis. In spite of this evidence of urethral obstruction in many cases no organic lesion can be demonstrated. Several cases with an ectopic ureteric opening into a seminal vesicle have been reported, and Jameson and Cooper (1955) record a similar case in which the contralateral kidney was absent.

In males the testes are invariably bilaterally undescended. The condition is compatible with survival to adult life, but most cases die in infancy or early childhood.

The condition is recognizable at birth by the lax abdominal wall with lateral bulging and wrinkling of the skin (Figs. 2 and 3). The bulging of the abdominal wall is more marked on crying and straining. The abdominal organs are easily palpable and a dilated and hypertrophied urinary tract may be visible through the wall as in Case 3.

The aetiology remains obscure, as it is undecided whether the dilatation of the renal tract is secondary to the absent abdominal muscles, or whether the muscles atrophy from pressure by the dilated bladder and ureters. In favour of the agenesis of the abdominal muscles being the primary defect is the fact that all cases of this condition which have been examined at necropsy have shown hypertrophy and dilatation of the bladder. Simple urinary obstruction with dilatation of the bladder, due to urethral valves or deformities of the bladder neck, is not associated with absent abdominal muscles. Housden (1934) has reviewed the various theories on the aetiology, and it can be said that little has been added to our knowledge since then.

The testes normally descend during the seventh month of intra-uterine life, but it is suggested that they are prevented from reaching the scrotum by the enlarged bladder and ureters.

The main danger to life is progressive renal

failure from recurrent or persistent urinary infections aggravated by the severe degree of hydronephrosis.

In other children (Case 4), the main complication appears in the lungs. Here progressive and frequent respiratory infections lead to permanent structural damage. These cases are now being kept alive longer by the use of modern antibiotics.

Treatment consists in trying to prevent these infections, both urinary and respiratory. Frequent emptying of the bladder helps to prevent urinary stasis, and a well-fitting abdominal corset assists the deficient or absent abdominal muscles. In America surgical relief of the urinary tract abnormalities is being increasingly undertaken (Mathieu, Goldowsky, Chaset and Mathieu, 1953). Riparetti and Charnock (1954) report a case in which an attempt was made to strengthen the abdominal wall by fascial transplants and excision of loose redundant skin.

In those children prone to repeated respiratory infections early and energetic treatment will help to prevent the inevitable onset of irreversible structural lung changes.

Summary

Four cases of absence of the abdominal muscles are presented, in three of which there was gross demonstrable abnormality of the urinary tract.

The clinical condition and the present unsatisfactory state of our knowledge of the aetiology and the complications are discussed.

It is recommended that cases of this condition should have a full investigation of the genito-urinary tract with a view to possible surgical treatment.

I wish to thank Dr. H. Everley Jones for permission to publish the first three cases and for helpful advice in the preparation of this paper. I also wish to thank Dr. J. V. C. Braithwaite for allowing me to include Case 4, and Mr. D. R. Paton for the photographs.

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BRITISH PAEDIATRIC ASSOCIATION

Proceedings of the Twenty-seventh Annual General Meeting

The twenty-seventh annual general meeting of the British Paediatric Association was held at The Old England Hotel, Windermere, from April 25 to 28, 1956.

BUSINESS PROCEEDINGS. Professor S. Graham took the Chair as the President, Professor F. M. B. Allen, had suffered a motor accident and was unable to be present. The following members were present:

E. C. Allibone, I. McA. Anderson, J. Apley, C. Asher, H. S. Baar, T. E. D. Beavan, M. Bodian, R. E. Bonham Carter, Frances Braid, J. V. Braithwaite, P. T. Bray, G. Brewis, R. W. Brookfield, Denis Browne, W. A. B. Campbell, W. H. P. Cant, I. A. B. Cathie, N. S. Clark, W. R. F. Collis, T. Colver, Beryl D. Corner, D. Court, J. Craig, W. S. Craig, Mildred Creak, J. Crooks, V. Mary Crosse, E. Dott, D. M. Douglas, A. C. Doyne Bell, S. Dundon, R. W. B. Ellis, J. L. Emery, P. R. Evans, J. O. Forfar, Isabella Forshall, A. White Franklin, D. Gairdner, W. F. Gaisford, W. H. Galloway, R. R. Gordon, C. F. Harris, E. W. Hart, C. C. Harvey, J. D. Hay, J. L. Henderson, W. Henderson, A. Holzel, D. V. Hubble, F. P. Hudson, J. H. Hutchison, R. S. Illingworth, N. M. Jacoby, Ursula James, H. Jolly, H. Everley Jones, F. F. Kane, J. J. Kempton, G. M. Komrower, R. Lightwood, J. Lorber, R. M. Mayon-White, P. MacArthur, D. MacCarthy, Agnes Macgregor, Helen M. M. Mackay, R. Mac Keith, F. J. W. Miller, A. A. Moncrieff, A. V. Neale, G. H. Newns, D. N. Nicholson, J. N. O'Reilly, W. H. Patterson, W. W. Payne, C. P. Pinckney, C. T. Potter, K. B. Rogers, R. A. Shanks, W. P. Sheldon, Ursula Shelley, Victoria Smallpeice, J. Forest Smith, R. E. Smith, J. Thomson, M. L. Thomson, J. P. M. Tizard, D. J. Waterston, A. G. Watkins, H. Parry Williams, T. Pearse Williams, Mary J. Wilmers, D. W. Winnicott, Winifred F. Young, S. Yudkin.

The report of the last annual general meeting was approved.

ELECTION OF OFFICERS. The following were elected:—

PRESIDENT: Professor J. Craig
TREASURER: Dr. R. Lightwood
SECRETARY: Dr. P. R. Evans
EXECUTIVE COMMITTEE (for three years):
Dr. A. C. Doyne Bell
Dr. D. MacCarthy
Dr. R. Mac Keith
Professor A. G. Watkins

(to replace Professor J. Craig, Dr. G. H. Newns, Dr. J. F. Smith and Dr. R. E. Steen).

ELECTION OF MEMBERS. The following members were elected:—

HONORARY MEMBER:
Professor F. M. B. Allen

CORRESPONDING MEMBERS:
Dr. J. H. Ebbs (Toronto)
Dr. Grover Powers (New Haven)
Dr. Joseph Stokes (Philadelphia)
Dr. H. C. Trowell (Uganda)
Professor C. C. de Silva (Colombo)

ORDINARY MEMBERS:
Dr. F. S. W. Brimblecombe
Dr. J. O. Craig
Dr. T. P. Mann
Dr. L. G. Scott
Dr. S. D. V. Weller
Dr. B. D. R. Wilson

The Treasurer's Report was received and approved.

The Executive Committee's report was received and approved, and is printed below:

Report of the Executive Committee, 1955-56

1. The Association will wish to congratulate Dr. Charles Harris on his appointment as Deputy Vice-Chancellor of the University of London, and Professor Stanley Graham on receiving the honorary degree of LL.D. (Toronto).

2. QUEBEC MEETING. At the joint meeting of the British Paediatric Association, the Canadian Paediatric Society and the American Pediatric Society in Quebec in June, 1955, the Association presented to the Canadian Society a carved gavel made from wood remaining from the old plane tree which stood in the grounds of The Hospital for Sick Children, Great Ormond Street.

3. HISTORY. The Executive expressed its gratitude to Dr. H. C. Cameron for writing and seeing through the press the history of the Association. Dr. R. Mac Keith was appointed Assistant Historian to the Association.

4. ARCHIVES OF DISEASE IN CHILDHOOD. Dr. W. W. Payne (re-elected), Miss Isabella Forshall and Dr. C. G. Parsons were nominated to serve on the Editorial Committee of the *Archives of Disease in Childhood*.

5. ANNUAL LECTURES. A questionnaire showed

that 59 members favoured continuing the Still Lectures, while eight opposed it; 44 were for and eight against the Windermere Lectures. Unless new funds are produced, the last Windermere Lecture will be given in 1956.

6. TROPICAL PAEDIATRICS, ETC. A new standing sub-committee has been set up to consider tropical paediatrics. Three visitors from the Commonwealth or Colonies have taken advantage of the offer of the Association to assist them to see what particularly interested them in paediatrics in the United Kingdom. At the invitation of the Executive Committee, the Colonial Office has nominated Dr. J. C. R. Buchanan to attend meetings as an observer when matters affecting the Colonies are to be discussed.

7. INTERNATIONAL PAEDIATRIC CONGRESS. A party of members of the American Academy of Pediatrics and their wives is stopping a short time in London on the way to the International Congress in Copenhagen, and it is hoped that many of our members (and their wives) will come to meet them at a dinner in London on July 18. The dinner is to be held at the Mansion House, by the kind permission of the Lord Mayor.

8. HYPERCALCAEMIA REPORT. A sub-committee was asked to investigate the incidence of hypercalcaemia in infants. Many members assisted in this enquiry and with remarkable celerity a report was prepared. In addition to indicating the incidence of the disease, it was shown that many infants were likely to receive more vitamin D than was generally realized. This is now being considered by the Ministry and the Medical Research Council.

9. ADMISSION OF CHILDREN TO HOSPITAL. A sub-committee has been set up to consider future policy regarding admission to hospital. It is thought that this needs consideration as older calculations of the needs for beds may not be apposite now that the incidence and treatment of certain illnesses have changed. Other organizations, such as the Nuffield Foundation, are also keenly interested in this subject.

10. HEIGHT AND WEIGHT COMMITTEE. The Height and Weight Survey Committee (Joint with Ministry of Health and Ministry of Education) was set up in 1948, and now that the results of the survey are being analysed the committee has been disbanded. Our thanks are due to its members (Dr. C. P. Pinckney, Dr. C. Asher, Dr. G. H. Newns) for their work.

11. MEMBERSHIP. The Executive Committee feels that it is time once again to consider future policy with regard to membership of the Association and there is little doubt that this will be one of the principal topics for discussion during the coming year.

12. OTHER CORRESPONDENCE. Among other matters considered, have been shortage of radiographers and of nurses, paediatrics in the medical curriculum, and whether the nation has enough paediatricians.

Rule 3 was altered to read: "The business of the Association shall be conducted by an Executive Committee consisting of a President, a President-Elect, a Treasurer, a Secretary and 12 Ordinary Members. All these officers shall be elected at an Annual General Meeting."

There was a discussion on the pros and cons of increasing the membership of the Association.

Scientific Meeting

In addition to the members noted above, Professor C. McNeil and the following new members, Dr. F. S. W. Brimblecombe, Dr. J. O. Craig, Dr. T. P. Mann, Dr. L. G. Scott and Dr. S. D. V. Weller, attended the scientific meeting, as well as 38 guests of whom 10 came from abroad.

Dr. L. Emmett Holt, Jnr., delivered the Windermere Lecture, his subject being 'The Adolescence of Nutrition'.

In two morning sessions the following communications were given:

DRS. R. LIGHTWOOD, F. S. W. BRIMBLECOMBE, and J. A. DAVIS (London) described 'A London Trial of Home Care for Sick Children with a Mobile Paediatric Team Supporting the Practitioner.' Although modern medical practice is based on a separation of the domiciliary and hospital services, there is a certain amount of overlapping: some practitioners hold hospital appointments, and there are a number of hospital home care projects. In America, private medical care being expensive, these projects provide for poor families and tend to displace the practitioner; in Britain the primary aim is to help the doctor in diagnosis and treatment, thus avoiding admission to hospital.

At St. Mary's Hospital a paediatric home care project provides rapid and comprehensive diagnostic help as well as a nursing service. Practitioners can call on a mobile team of hospital paediatricians and nurses to help in the care of children who would otherwise be admitted to hospital. From April, 1954, to March, 1956, 582 cases, mostly young children, have been handled, including many of the major medical illnesses, and it has been possible to apply the usual hospital procedures for diagnosis and treatment. The aims, in order of importance, are (1) improved practitioner/hospital liaison; (2) avoidance of unhappiness and cross-infection; and (3) reduction of cost while maintaining standards.

In an urban area where there is no shortage of beds, the service is gaining popularity and doctors are using

it more and more, finding that it helps to keep them in touch with hospital practice and to share clinical responsibility without losing it. There are also advantages in bringing hospital staff into contact with domiciliary work. The treatment of a patient in the environment where his illness has been acquired can frequently provide opportunities for correcting social and environmental causes.

DR. W. M. GIBSON (Montreal). 'Lingular Biopsy Assessment.' Lingular biopsy is a relatively simple technique for obtaining lung tissue during thoracotomy. Control studies have shown that the vessels seen in such biopsies are representative of those throughout the lung. Fifty lingular biopsies were taken at The Hospital for Sick Children, Great Ormond Street, from 99 cases of simple or complicated patent ductus arteriosus. Satisfactory studies of the vessels could be made in 48 cases. Definite changes attributable to pulmonary hypertension were found in the vessels in 23 cases; the most frequent alterations in the vessels consisted of hyperplasia and hypertrophy of the medial muscle coat and duplication of associated elastic tissue.

Among the 48 cases, pressure studies were available in 24 instances. In this group, there was a direct relationship between mean pulmonary pressure, and the degree of the histological changes. It was notable that the severest lesions, consisting of intimal thickening or necrotizing changes in the vessel wall, were only seen in children over 3 years of age.

The present study confirms the value of lingular biopsy in diagnosing the presence and degree of pulmonary hypertension.

DR. GAVIN C. ARNEIL (Glasgow). 'Vasopressic Factors in Stored Plasma.' It has previously been demonstrated that plasma from cases of acute nephritis with hypertension developed greater vasopressic activity than plasma from normal subjects when tested in the debenamized rat. It is now noted that angiotonin may be accurately assayed by this method and that incubation of normal plasma at 37° C. results in marked pressor activity appearing. This rise in pressure should not be due to an adrenaline, or serotonin or an organic amine; these are blocked by dibenamine. The active plasma was compared with samples of plasma to which vasopressin or angiotonin had been added. The former is differentiated easily, since sodium thioglycollate destroys its activity. The latter differs in pattern of contraction induced, both in the rat when tested on guinea-pig ileum, and probably in the site of action. Plasma becomes activated by such incubation even when thrombocytopenic; neither serum nor plasma in which the platelets have been traumatized by agitation possesses pressor activity until incubated; clotting and platelet disintegration are not, therefore, likely to be implicated.

During the preparation of plasma by the blood transfusion service, this biological fluid is retained at room temperature for considerable periods. Eight specimens of blood bank plasma were tested and each found to contain pressor activity equivalent to more than 100 cat units of angiotonin per 100 ml. This is sufficiently potent to make pharmacological activity *in vivo* seem likely, if man is as sensitive as rat to the vasopressic factor and plasma infused as rapidly.

DR. J. H. HUTCHISON (Glasgow). 'Hereditary Transmission of Sporadic Cretinism with Goitre.' The pedigree of a family group of itinerant tinkers in which there had appeared 10 goitrous cretins with four sibships, and four cases of Werdnig-Hoffmann spinal paralysis in another sibship was shown. The pedigree had been traced back for 160 years and included five generations. The amount of consanguineous mating had been remarkable and was due to the peculiar isolation of these people from the rest of the community. The pedigree satisfied the usual criteria of simple recessive inheritance. This mode of inheritance was made the more likely by the very frequent occurrence of familial incidence and consanguinity in other similar cases of goitrous cretinism which have been described in the British and American literature. Five other cases of goitrous cretinism which had been observed in Scotland were described. They belonged to two separate families, also tinker-people, and it seemed probable that they owed their condition to the same autosomal recessive gene occurring in the homozygous state. Radioactive iodine studies on these patients had produced evidence to suggest that, in this group, the state of goitrous cretinism was due to an inborn deficiency of the enzyme dehalogenase. As a result, the iodotyrosyl groups within the thyroid gland were not de-iodinated and large amounts of diiodotyrosine were lost from the gland into the blood stream. In none of these cases was there any deficiency of iodine-intake or ingestion of goitrogens.

DR. J. W. FARQUHAR (Edinburgh). 'Combined Management of the Diabetic Pregnancy: A Review of 123 Consecutive Pregnancies.' The foetal loss rate in 123 diabetic pregnancies (of which three were twin pregnancies) studied in Edinburgh from 1948 to 1955 is much smaller than that which had prevailed previously. It was contended that the improvement was the direct result of careful combined work by a team consisting of physician, obstetrician and paediatrician. The overall foetal loss was 29·4% and the viable foetal loss was 22·6%. In 84 cases, however, where the obstetric care was judged to have been adequate, the loss was only 16·6%. Inadequate antenatal obstetric care, together with poor diabetic control, made a very lethal combination, the viable foetal loss being 60%. Premature intrauterine death accounted for 17 losses and remains the greatest problem. The pathology of the eight neonatal deaths was varied but definite. Abnormal clinical behaviour was shown by 39 of the 97 babies who were born alive. The clinical features may be divided broadly into dyspnoea which lasts for hours or days, and apnoea which is brief but may be recurrent. The former is not necessarily due to respiratory pathology and is often progressive to death. The apnoeic attacks are alarming, but not fatal. Evidence was offered to support the contention that a factor additional to prematurity was responsible. Brief mention was made

of paediatric management of the newborn, of congenital malformations and of the risk of diabetes mellitus in the offspring.

DR. H. MCC. GILES (London). 'Nephrotic Syndrome in the Newborn.' Three cases were presented in which the nephrotic syndrome developed during the first few weeks of life. Two were brother and sister, and the offspring of first cousins; the parents of the third were second cousins once removed. There were healthy sibs in both families, and no other cases of renal disease were known in either. The infants died at 6, 5 and 2½ months respectively. At necropsy, the most striking feature was gross renal tubular damage with only minor glomerular lesions; these changes varied in severity with the age at death.

Alcohol-fixed material from the liver, spleen, kidney and bone-marrow in each case showed anisotropic crystals which were probably amino-acid in nature, although the amount present was insufficient for positive identification. Microdissection of the kidneys (Dr. E. M. Darmady) showed narrowing of the juxta-glomerular portion of the tubule, recalling the 'swan-neck' lesion found in the Fanconi syndrome; in the third infant the changes were less clearly defined.

It was concluded that all three cases suffered from the same disorder, which involved primarily the renal tubules and was perhaps inherited as a recessive characteristic.

DR. R. J. PUGH and DR. H. BLYTH (Leeds). 'Childhood Muscular Dystrophy: a Combined Clinical and Genetic Appraisal.' A field survey has been attempted from Leeds over the last four years with the object of tracing as many examples as possible of childhood muscular dystrophy in order to learn what clinical types are recognizable and how they are inherited.

Ninety-four patients developing symptoms due to muscular dystrophy during the first 12 years of life have been examined in their homes and genetic histories recorded. The vast majority (86) represent the familiar childhood type, but separate into two groups by virtue of differing severity and rate of progress, while the remaining cases are made up of facio-scapulo-humeral (five) and limb girdle (three) variants.

Some features of the two more common types are summarized:

	Severe	Mild
Number	57	29
Sex	All males	15 females
Onset	All in infancy	20 in infancy
Walking	70% by 18 months	70% by 18 months
Unable to walk	Before 11th birthday	After 11th birthday
Scholarship	Subnormal in 21	Subnormal in 3
Muscular pseudo-hypertrophy	Gross in all	Inconspicuous in 12
Inheritance	Sex-linked recessive	Various

An appreciation of the likely category of an affected child may influence educational and occupational management and allow of a more accurate prognosis.

DR. CONSTANCE FORSYTH (Dundee). 'Serum Protein Electrophoresis: Studies in Rheumatic Fever, Still's Disease and Acute Nephritis.' By paper electrophoresis the serum proteins may be separated into albumin and α_1 α_2 β and γ globulin bands. The method provides greater detail than the albumin:globulin ratio and more selective information than the blood sedimentation rate.

In this study, the paper strips were prepared using the Flynn and de Mayo technique. As a preliminary, the normal alterations in pattern for children between birth and 12 years were established, and the changes in acute and chronic infections were investigated. Serial studies were then made during the course of the illness in 20 children with rheumatic fever, 15 with Still's disease and 24 with acute nephritis and related to their clinical progress and the blood sedimentation rates. As in infections, increases in α_1 α_2 and γ globulins reflected the stage and severity of the disease; such increases, however, did not always run parallel with fluctuations in the blood sedimentation rate and sometimes persisted after the latter had returned to normal. Serum electrophoresis may thus provide an additional guide to the duration of treatment with salicylates, cortisone or simple bed rest.

The following papers were also read: 'Regeneration of Bone Marrow in Aplastic Anaemia' (Dr. C. Gasser, Zurich); 'Some Observations on the Treatment of Acute Leukaemia in Childhood' (Dr. R. B. Thompson, Newcastle); 'Histological Aids to the Diagnosis and Management of Hirschsprung's Disease' (Dr. M. Bodian, London); 'The Diagnosis and Treatment of Persisting Hyperelectrolytaemia with Renal Dysfunction in Infants' (Drs. W. F. Young, Bernard Levin and Alex Russell, London); 'British Freeze-dried B.C.G. Vaccine: Preliminary Clinical Trials' (Dr. J. Lorber, Sheffield).

BOOK REVIEWS

Nursing Care of the Newly Born Infant. By W. S. CRAIG, in collaboration with M. F. G. BUCHANAN, R. J. PUGH and MISS M. PATTULO, with a chapter on Mothercraft by MISS M. J. W. TAYLOR. (Pp. 472; 226 illustrations (24 in colour). 35s.) London and Edinburgh: E. & S. Livingstone. 1955.

This is a comprehensive survey of the newborn infant, its development before and after birth, its appearance and behaviour, its feeding and management and the maladies, small and large, to which it is prone. It is intended primarily for midwives, and in writing it the authors have not just composed a medical book in a minor key, but have throughout borne in mind the special requirements of the midwife and presented her with clear and detailed advice on almost any problem with which she may be faced. The book manages to be up to date without being controversial and uncontroversial without being dull. The numerous diagrams and photographs add not only to the palatability but also to the nutritive value of the book. Some of the colour photographs, however, whilst striking, are not altogether convincing.

Although this work is clearly designed for the midwife, the lack of any good modern textbook on the newborn will extend its sale to medical practitioners, to whom it can be confidently recommended.

Finally, the reviewer agrees with the authors that the frontispiece speaks for itself.

Child Health and Development, 2nd ed. By various authors, edited by R. W. B. ELLIS. (Pp. x+525; 81 figures. 42s.) London: J. & A. Churchill. 1956.

The first edition of this book appeared in 1947, before the advent of the Health Service or the Children Act of 1948, to mention two only of the big changes in legislation and administration which have occurred since then. In consequence the present volume is almost a new book, being extensively revised and with much new material. The editor's own new contributions include an excellent chapter on punishment and another on child health in the tropics. Dr. H. P. Tait now deals most competently with many of the present-day services for children, and another specially valuable new chapter is on prenatal development by Professor I. Donald. The very large increase in size is to be regretted, but it is difficult to suggest what should be pruned. Miss Anna Freud's two chapters (as in the first edition) are a little sectarian for everyone's taste and this may put readers off acquiring important information on emotional development. Professor Ellis has wisely drawn in many of his fresh recruits from his present Scottish colleagues, largely acquired since the first edition, but their views and statements are broad enough to cover the British Isles where this book should continue to be a valuable contribution to child health, and a useful work of reference.

Sick Children, 7th ed. By DONALD PATERSON. Revised by Reginald Lightwood, with the assistance of F. S. W. Brimblecombe. (Pp. ix+593; 82 figures, 16 plates. 42s.) London: Cassell. 1956.

There are by now very many books on paediatrics available to the consumer; textbooks, handbooks, revision books, synopses, books directed to the general practitioner, to the specialist, to the radiologist, to the nurse, to the physiotherapist and others; in English, French, German, Italian, Spanish, and so on. It must be assumed that all have their adherents or followers, or so many would not be produced. Many are destined to flower briefly and be seen no more, while others, Phoenix-like, are re-born in new and improved fashion as often as advances in their subject necessitate. Such a one of these is Paterson's *Sick Children*, the 7th edition of which, coming nine years after its predecessor, has been almost completely revised by Dr. Lightwood.

The remaining cohorts of admirers of Dr. Paterson, and there are very many in this country who came under his influence, will be delighted that the style and format of his book have been so successfully retained in the latest version. As common things tend to occur commonly, so the emphasis on the diagnosis and treatment of the commoner ailments of childhood is always to the fore—rarities are left to the weightier and more comprehensive tomes. New sections have been created by Dr. Cicely Williams on the ailments of children in the tropics and by Dr. J. P. M. Tizzard on disorders of the nervous system. There are also most useful and up-to-date appendices on the antibiotics and other drugs, and vitamins, electrolytes and ossification data.

Those accustomed to using *Sick Children* will scarcely recognize this latest version, but whatever any previous edition has been to them this one will be, and more so.

German Medical Journal, Vol. I. Published by Georg Thieme, Stuttgart. 1956. (Annual subscription £1 10s.; DM. 17.60.)

Those who have difficulty in reading the German language will welcome the appearance of a new journal—the *German Medical Journal*. Its purpose is to present an overall view of German medicine in the English language and the first number contains half-a-dozen original articles and a series of medical snippets. It is proposed that the most important articles from the *Deutsche Medizinische Wochenschrift* will be translated (selection of the articles for translation will be a thankless task) and there will be editorials, reviews, abstracts and the like.

Whether this translation of selections from one German journal will enable the reader to obtain a complete picture of German medicine is problematical, but it is a worthwhile undertaking which, if successful, will be invaluable. This one more journal to read is to appear monthly and will cost £1 10s. a year.